#4

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Dated 28 February 2001

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
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1. Your reference

MPW/P21125GB

2. Patent application number
(The Patent Office will fill in this part)

06 NOV 1998 **9824393.4**

3. Full name, address and postcode of the or of each patent applicant *(underline all surnames)*

EISAI LONDON RESEARCH LABORATORIES LIMITED
BERNARD KATZ BUILDING
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GOWER STREET
LONDON WC1E 6BT
UK

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

06347256001

4. Title of the invention

PHARMACEUTICAL COMPOSITIONS AND THEIR USES

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

KILBURN & STRODE
20 RED LION STREET
LONDON
WC1R 4PJ

Patents ADP number *(if you know it)*

125001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application number	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

YES

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body. See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	:	
Description	:	86
Claim(s)	:	3
Abstract	:	1
Drawing(s)	:	2

10. If you are also filing any of the following, state how many against each item.

Priority documents	:
Translations of priority documents	:
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	:
Request for preliminary examination and search *(Patents Form 9/77)*	:
Request for substantive examination *(Patents form 10/77)*	:
Any other documents *(please specify)*	:

11. I/We request the grant of a patent on the basis of this application.

Signature: Kilburn & Strode

Date: 6/11/98

Kilburn & Strode

6 November 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

Martin P White
Tel: 0171-539 4200

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

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Pharmaceutical c mpositions and their uses

The present invention relates inter alia to the treatment of demyelinating disorders.

The majority of excitatory synaptic responses in mammalian CNS are elicited by amino acids such as L-glutamate or L-aspartate and are mediated by four different receptor subtypes. Three of these receptors are coupled to ionophores and are known as the N-methyl-D-aspartate (NMDA), the AMPA α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate), and the kainate receptors. The fourth receptor subtype is linked to phosphoinositol metabolism and is known as the metabotropic glutamate receptor.

The NMDA receptor is coupled to high conductance channels permeable to Na^+, K^+, and Ca^{2+} (McBain CJ, Mayer M (1994): N-Methyl-D-aspartic acid receptor structure and function, Physiol. Rev., **74:**723-760). It is modulated by glycine (coagonist) and polyamines (positive modulator) and is blocked in a use- and voltage dependent manner by Mg^{2+}. The functional NMDA receptor is thought to be formed as a pentameric subunit assembly consisting of subunit selection from NR1 (eight isoforms) and NR2 (four isoforms) families (Hollmann M, Heinemann S (1994): Cloned glutamate receptors, Annu. Rev. Neurosci. **17:**31-108). The type of subunits forming the NMDA channel determine its biophysical properties and physiological function (Schöpfer R, Monyer H, Sommer B, Wisden W, Sprengel R, Kuner T, Lomeli H, Herb A, Kohler M, Burnashev N (1994): Molecular biology of glutamate receptors, Prog. Neurobiol. **42:**353-357). The AMPA and kainate receptors are permeable to Na^+ and K^+ (Hollmann and Heinemann, 1994 [*supra*]). AMPA receptor-dependent ion channel is formed from four different subunits designated as GluR1 to GluR4 (in two alternative splice variants - flip and flop) in a tetrameric subunit assembly (Hollmann and Heinemann, 1994 [supra]; Rosenmund C, Stern-Bach Y, Stevens C (1998): The tetrameric structure of a glutamate receptor channel, Science **280:**1596-1599). Pharmacological properties of AMPA receptor-dependent ion channels are determined by

the selection of subunits. Channel assemblies lacking GluR2 subunits are permeable to Ca^{2+} in addition to Na^{+}- and K^{+}-permeability (Hollmann and Heinemann, 1994 [*supra*]). *In situ* hybridization has revealed different expression of glutamate receptor subunits throughout the brain and during development (Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg P (1994): Developmental and regional expression in the rat brain and functional properties of four NMDA receptors, Neuron **12**:529-540).

In contrast to the well documented role of glutamate in the pathogenesis of neuronal degeneration resulting from hypoxia/ischemia, hypoglycemia, convulsions and head or spinal cord trauma, no clear link has been established between glutamate-mediated cell death and demyelinating disorders. Many demyelinating disorders have previously been resistant to therapy. Furthermore, until recently, the treatment of human demyelinating disorders has relied exclusively on the use of immunosupressive agents such as corticosteroids and cyclophosphamide, which although providing limited benefit to patients, can be associated with potentially serious side effects. The introduction of interferon preparations has provided efficacy in the treatment of certain demyelinating disorders (e.g. multiple sclerosis). However, as benefits are apparent in only a portion of the subgroup of patients classified as suitable for tratment, then management of the disease is still insufficient with such preparations.

The present inventors have now provided evidence in support of the involvement of glutamate in the pathogenesis of demyelinating disorders. They have established a link between neuronal demyelination and glutamate-mediated cell death.

The present invention represents a major advance over prior art methods in the treatment of demyelinating disorders.

According to an aspect of the present invention, there is provided the use of an inhibitor of the interaction of glutamate with the AMPA receptor complex in the manufacture of a medicament for treating a demyelinating disorder.

The term "inhibitor of the interaction of glutamate with the AMPA receptor complex" is used herein to include moieties that bind to the AMPA receptor or to glutamate so as to prevent or reduce the binding of glutamate to its binding site on the AMPA receptor. Such moieties may bind in a competitive or non-competitive manner. They are referred to herein as "antagonists" of the binding of glutamate to the AMPA receptor. A skilled person is able to identify substances that may be useful as antagonists of the present invention by binding studies. For example, the AMPA receptor, a part thereof including said glutamate binding site, or a glutamate molecule can be used to screen for substances that bind thereto, preferably in a highly specific manner. Such binding studies can be part of a screening program for identifying or designing potential therapeutic agents.

The term "inhibitor of the interaction of glutamate with the AMPA receptor complex" also includes moieties that prevent a signal being transmitted that would otherwise occur when glutamate binds to the AMPA receptor. Preferred such moieties are AMPA receptor channel blockers. The term "AMPA receptor channel blocker" is used herein to refer to moieties that reduce the permeability of ion channels associated with the AMPA receptor in vivo (preferably to Na^+, K^+ and/or Ca^{2+} ions).

Various antagonists and AMPA receptor channel blockers that are within the scope of the present invention will now be described in greater detail:

Antagonists

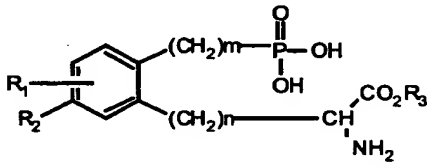
The antagonists of the present invention include L-glutamate derivatives such as e.g. L-glutamic acid diethylester, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate derivatives such e.g., a-amino-3-hydroxy-5-tert-buthyl-4-isoxazolepropionic acid, quinoline, quinoxaline, quinoxalinedione, quinazolinone, phenylpyridazino-indole-1,4-dione, indeno-pyrazinone, indeno-pyrazine-carboxylic acid, indolo-pyrazinone, imidazo-pyrazinone, amino-phenyl-acetic acid, benzothiadiazine, 4-hydroxypyrrolone, 4-hydroxy-pyrrolo-

pyridazinone, quinolone, amino alkanoic acid, isatin, nitroquinolone, phenyl-azolophthalazine, amino- or desamino- 2,3-benzodiazepine, 2,3-benzodiazepin-4-one, β-carboline-3-carboxylic acid, alkoxy-phenyl-benzodiazepine, acetyl-aminophenyl-dihydro-methyl-dioxolo-benzodiazepine, oxadiazol, isatinoxime, decahydroisoquinoline, and sulphamate.

Further substances that may be useful as antagonists are listed below:

List of Antagonists

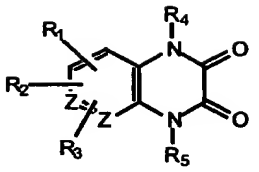
(1) ω-[2-(Phosphonoalkyl)phenyl]-2-aminoalkanoic acids (I) in WO 93-05772 as shown below:

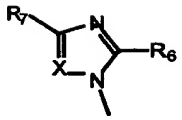


(I)

ω-[2-(Phosphonoalkyl)phenyl]-2-aminoalkanoic acids represented by formula (I), wherein n and m independently are 0, 1, 2 or 3; R^1 is selected from the group consisting of hydrogen and R^2; R^2 is selected from the group consisting of hydrogen, halogen, halomethyl, nitro, amino, alkoxy, hydroxyl, hydroxymethyl, C_1 to C_6 lower alkyl, C_7 to C_{12} higher alkyl, aryl and aralkyl, wherein if R^2 is hydrogen, R^1 is not hydrogen; R^3 is selected from the group consisting of hydrogen and C_1 to C_6 lower alkyl; the stereoisomers thereof in their resolved or racemic form, and pharmaceutically acceptable salts thereof.

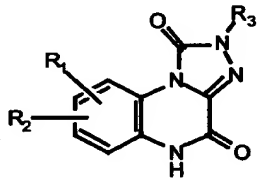
(2) Fused pyperazine derivatives in WO 92-07847 as shown below:

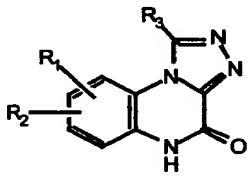

(Ia)


(1a)

A pyperazine derivative represented by general formula (Ia) wherein Z represents C or N, provided that two Zs are not N atoms at the same time; R^1 represents (1a) wherein X represents N or R^8C, R^6 represents H or alkyl, and R^7 and R^8 represent each H, alkyl, nitro or phenyl, or alternatively R^7 and R^8 are combined together to represent butadienylene or 1,4-butylene; R^2 and R^3 represent each H, F, cyano, acyl, nitro, alkyl, morpholino or R^1; R^4 and R^5 represent each H, hydroxy, alkyl, cycloalkyl, heterocycle, phenyl or Y-substituted alkyl; Y represents hydroxy, acyloxy, F-substituted methyl, cycloalkyl, tetrahydrofuryl, carboxyl, alkoxy carbonyl or NR^9R^{10}; and R^9 and R^{10} represent H or alkyl, or alternatively R^9 and R^{10} are combined together to represent a 5- or 6-membered cyclic group which may contain oxygen atom(s).

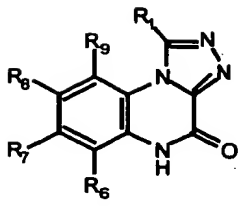
(3) Triazoloquinoxalin-1,4-diones (I) and (II) in WO 93-06103 an shown below:


(I)


(II)

Quinoxaline compounds represented by formula (I) or (II), wherein R^1 and R^2 are independently hydrogen, C_{1-6}-alkyl, halogen, NO_2, NH_2, CN, CF_3, $SO_2NR^4R^5$ wherein R^4 and R^5 are independently hydrogen or C_{1-6}-alkyl, or COR^6 wherein R^6 is C_{1-6}-alkyl; and R^3 is hydrogen, C_{1-6}-alkyl or CF_3, and compositions thereof.

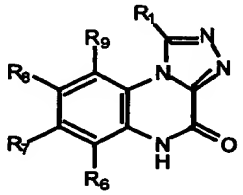
(4) [1,2,4]Triazolo[4,3-a]quinoxalinone derivatives (I) in WO 96-08493 A1 as shown below:



(I)

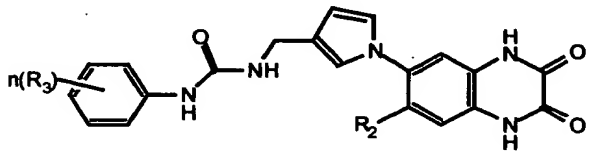
[1,2,4]triazolo[4,3-a]quinoxalinone compounds of general formula (I) wherein R^1 is POX'X" or alkyl substituted with COX' or POX'X", and X' and X" independently are hydroxy or alkoxy, and R^6, R^7, R^8 and R^9 independently are hydrogen; alkyl; halogen; NH_2; NO_2; CN; CF_3 $SO_2NY'Y"$ OR COZ' wherein Z' is NY'Y" or alkyl and Y' and Y" independently are hydrogen or alkyl; triazolyl; imidazolyl substituted with phenyl or alkyl.

(5) [1,2,4]Triazolo[4,3-a]quinoxalinone derivatives (I) in WO 96-08492 A1 as shown below:



[1,2,4]triazolo[4,3-a]quinoxalinone compounds of general formula (I) wherein R^1 is POX'X" or alkyl substituted with COX' or POX'X" and X' and X" independently are hydroxy or alkoxy, and R^6, R^7, R^8 and R^9 independently are hydrogen; alkyl; halogen; NH_2, NO_2, CN, CF_3, SO_2NY'-Y", COZ' wherein Z' is NY'Y" or alkyl and Y' and Y" independently are hydrogen or alkyl; triazolyl; imidazolyl, piperidino, piperazinyl, morpholino or thiomorpholino; all rings optionally being substituted.

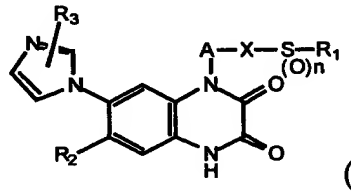
(6) Pyrrolylquinoxalindiones (I) in WO 97 49701 as shown below:



(I)

Pyrrolylquinoxalindiones of formula (I) and their tautomeric and isomeric forms and their physiologically acceptable salts, in which R^1 is hydrogen, C_1-C_6 alkyl, substituted by hydroxyl or carboxyl, R_2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, a chlorine, fluorine or bromine atom, a trihalogen methyl, cyano, or nitro group or $SO_2C_1C_4$ alkyl, R^3 is COOH or a radical hydrolysable to form the carboxyl group, and n is 1 or 2.

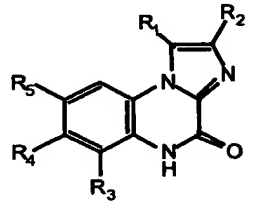
(7) Imidazole-substituted quinoxalinedione derivatives (I) in WO 97-46555 as shown below:



(I)

Substituted imidazole quinoxalinedione derivatives represented by general formula (I), wherein each symbol has the following meaning: A: $(CH_22_?)_m$ or Ph-$(CH_2)_p$ (Ph being phenyl); X: oxygen or NR^4; R^1 : hydrogen, hydroxy or triazolyl, provided that X may be a bond when R^1 is triazolyl; R^2 : hydrogen, nitro, halogenated lower alkyl, cyano, amino, mono - or di (lower alkyl)amino, or halogeno; R^3 and R^4; : the same or different and each representing hydrogen or lower alkyl; n: 0, 1 or 2; m: an integer of 2 to 6; and p: an integer of 1 to 6.

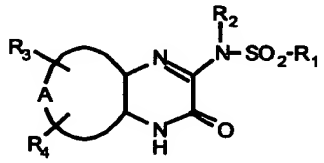
(8) Heterocyclically substituted imidazoloquinoxalines (I) in WO 97-34896 as shown below:



(I)

Imidazoloquinoxalines of formula (I), wherein R^1 to R^4 have the meanings given in the description in the corresponding patent (WO 97-34896) and R^5 is a five-member optionally substituted heterocycle with between 1 and 4 nitrogen atoms or with 1 or 2 nitrogen atoms and an oxygen or sulphur atom, or an R^6-substituted phenyl ring.

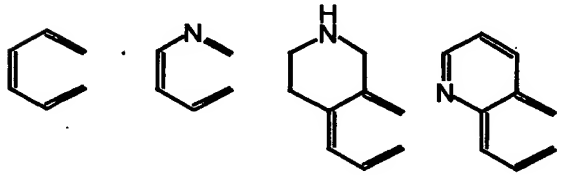
(9) Quinoxaline derivatives (I) in WO 97-32858 as shown below:



(I)

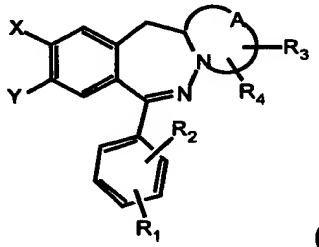
Quinoxaline derivatives of the formula (I) wherein R^1 is alkyl, halo (lower) alkyl, amino, aryl or heterocyclic group, R^2 is hydrogen or lower alkyl, R^3 and R^4 are each independently hydrogen, cyano, nitro, halogen, lower alkyl, halo (lower) alkyl, lower alkoxy, halo (lower) alkoxy, di (lower) -alkylamino, aryl which may have one or more substituents (s), heterocyclic group which may have one or more substituents (s), lower alkylthio which may have one or more substituents (s), heterocyclicthio, lower alkylsulfonyl, lower alkylaminosulfonyl, or heterocyclicsulfonyl, a group of the formula:

A is the group of the formula:



It is to be noted the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom (s) and double bond, and all of such isomers and a mixture thereof are included. It is further to be noted that isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention. It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

(10) Condensed 2,3-benzodiazepine derivatives (I) in WO 97-28163 as shown below:

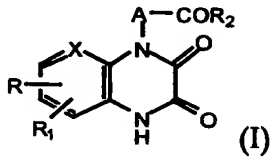


(I)

2,3-Benzodiazepine derivatives of the formula (I) wherein R^1 and R^2 are identical or different and hydrogen, C_1-C_6-alkyl, nitro, halogen, cyano, the group -NR^8R^9, -O-C_{1-4}-alkyl, -CF_3, OH or C_{1-6}-alkanoyloxy; R^3 and R^4 are identical or different and hydrogen, halogen, C_1-C_6-alkoxy, hydroxy, thiocyanate, C_1-C_6-alkylthio, cyano, $COOR^{12}$, $PO_3R^{13}R^{14}$, C_1-C_6-alkanoyl, C_1-C_6-alkanoyloxy, eventually with C_1-C_4-alkoxy or phenyl-substituted C_{2-6}-alkynyl, eventually with C_{1-4}-alkoxy or phenyl-substituted C_{2-6}-alkenyl, eventually with halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-thioalkyl, NR^{10}-R^{11}-substituted C_1-C_6-alkyl, C_{3-7}-cycloalkyl or eventually a substituted aryl- or hetaryl-rest; R^8 and R^9 are identical or different and hydrogen, C_1-C_6-alkyl or the group-CO-C1-6-alkyl; R^{10} and R^{11} are identical or different and hydrogen, C_1-C_6-alkyl or C_{1-6}-alkanoyl or together with the nitrogen atom will bild a 5-7 branched saturated heterocyclus, which will contain and can be susbtituted with a further oxygen-, sulfur or nitrogen atom; R^{12}, R^{13}, R^{14} are identical or differnt

and H or C_1-C_6-alkyl; X hydrogen or halogen; Y C_{1-6}-alkoxy or X and Y together - O-(CH2)n-O-; n means 1,2 or 3 and A together with the nitrogen will form a saturated or an unsaturated 5 armed heterocyclus, which can contain 1-3 nitrogen atoms and/or a oxygen atom and/or one or two carbonyl groups or their isomers or physiological salts thereof.

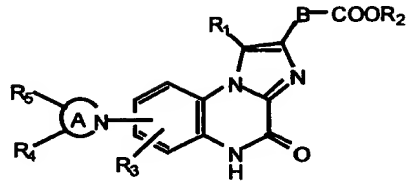
(11) 1,2,3,4-Tetrahydroquinoxalindione derivatives (I) in WO 96-10023 as shown below:



(I)

A 1,2,3,4-tetrahydroquinoxalindione derivative represented by general formula (I) or a salt thereof, an NMDA-glycine receptor and/or AMPA receptor antagonist and a kainate neurocytotoxicity inhibitor each containing the same, and a medicinal composition comprising the above-mentioned compound and pharmaceutically acceptable carriers: wherein X represents N or CH; R represents imidazolyl or di(lower alkyl)amino; R^1 represents (I) halogeno, nitro, cyano, carboxy, amino, mono- or di(lower alkyl) amino, lower alkanoyl, lower alkythio, lower alkylsulfinyl, lower alkylsulfonyl, or carbamoyl, (2) lower alkyl or lower alkoxy which may be substituted by halogeno, carboxy or aryl, or (3) phenyloxy which may be substituted by lower alkoxycarbonyl or carboxy; R^2 represents hydroxy, lower alkoxy, amino, or mono- or di(lower alkyl)amino; and A represents optionally substituted alkylene or -O-B- (B being lower alkylene); provided the case wherein R represents imidazolyl, R^1 represents cyano, A represents ethylene and R^2 represents hydroxy is excepted.

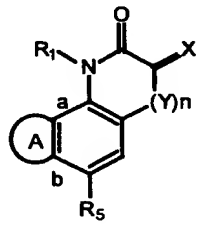
(12) New heterocyclic substituted imidazoloquinoxalinones (I) in WO 96-10572 as shown below:



(I)

Imidazoloquinoxalinones of the formula (I), in which R^1 stands for hydrogen, branched or linear C_{1-5}-alkyl or a phenyl, pyridyl or thienyl group possibly substituted by one to two chlorine atoms, a trifluoromethyl, a nitrodioxy or a methylene dioxy group; R^2 stands for hydrogen, C_{1-5}-alkyl or C_{3-8}-dialkylaminoalkyl; R^3 stands for a chlorine or bromine atom, a trifluoromethyl, cyano or nitro group; A stands for a five-membered heterocycle with 1-4 nitrogen atoms or 1-2 nitrogen atoms and one oxygen or sulphur atom possible substituted by R^4 and R^5; the radicals R^4 and R^5, that may be the same or different, stand for hydrogen, C_{1-5}-alkyl, C_{1-5}-hydroxyethyl, phenyl, phenyl substituted by a chlorine atom, a trifluoromethyl or nitro group, -CHO, -COOH, -COO-C_{1-5}-alkyl, -CH_2-NR^6R^7 (in which R^6=H, C_{1-5}-alkyl, R^7=H, C_{1-5}-alkyl), -CH_2-NH-CO-R^8 (in which R^8=C_{1-5}-alkyl, phenyl, a phenyl group or an heteroaryl group possibly substituted by a chlorine atom of a nitro or trifluoromethyl group) or -CH_2-NHCONHR^8, and B stands for a bond or a C_{1-5}-alkylene chain. Also disclosed are the tautomer and isomer forms of these compounds, as well as their physiologically compatible salts.

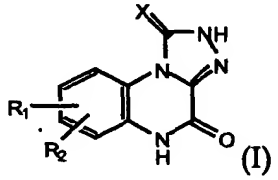
(13) Fused indole and quinoxaline derivatives (I) in WO 9608495 A1 as shown below:



(I)

Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein: R^1 is hydrogen, alkyl or benzyl; X is O or NOR^2, wherein R^2 is hydrogen, alkyl or benzyl; Y is N-R^4 wherein R^4 is hydrogen, OH or alkyl; n is 0 or 1; R^6 is phenyl which is substituted one or more times with substituents selected from the group consisting of $SO_2NR'R''$, CONR'R", and COR'" wherein R' and R" each independently are hydrogen, alkyl, or $-(CH_2)_p$-W, wherein p is 0, 1, 2, 3, 4, 5, or 6, and W is hydroxy, amino, alkoxycarbonyl, or phenyl which may be substituted one or more times with substituents selected from the group consisting or halogen, CF_3, NO_2, amino, alkyl, alkoxy or methylenedioxy; or wherein R' and R" together are (CH_2),Z(CH_2), wherein r and s each independently are 0, 1, 2, 3, 4, 5 or 6 and Z is O, S, CH_2 or NR"" wherein R"" is hydrogen, alkyl, or $-(CH_2)_p$-W, wherein p is 0, 1, 2, 3, 4, 5 or 6, and W is hydroxy, amino, alkoxycarbonyl, or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, NO_2, amino, alkyl, alkoxy or methylenedioxy; and wherein R"' is hydrogen, alkyl, alkoxy or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, NO_2, amino, alkyl, alkoxy or methylenedioxy; A is a ring of five to seven atoms fused with the benzo ring at the positions marked a and b.

(14) [1,2,4]Triazolo[4,3-a]quinoxaline compounds (I) in WO 94-26746 as shown in below:

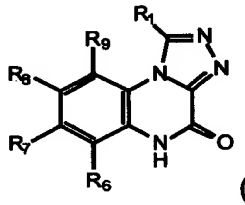


(I)

[1,2,4]Triazolo[4,3-a]quinoxaline derivatives of general formula (I) wherein one of R^1 and R^2 is a 5- or 6-membered N- containing heterocyclic ring optionally

substituted, or a fused ring system comprising a 5- or 6-membered N-containing heterocyclic ring optionally substituted; and the other of R^1 and R^2 is H, alkyl, alkoxy, halogen, NO_2, NH_2, CN, CF_3, COC_{1-6}-alkyl or $SO_2NR'R''$, wherein R' and R'' are independently H or alkyl and X is O or S; and pharmaceutically acceptable salts thereof.

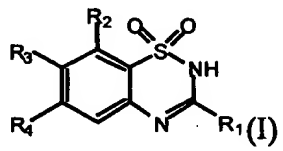
(15) [1,2,4]Triazolo[4,3-a]quinoxaline derivatives (I) in WO 94-21639 as shown below:



(I)

Quinoxaline compounds of general formula (I) wherein R1 is COX', POX'X'' or alkyl substituted with COX'' OR POX'X'', and X' and X'' independently are hydroxy or alkoxy, and R^6, R^7, R^8 and R^9 independently are hydrogen, alkyl, halogen, NH_2, NO_2, CN, CF_3, $SO_2NY'Y''$ or COZ' wherein Z' is NY'Y'' or alkyl and Y' and Y'' independently are hydrogen or alkyl, triazolyl, imidazolyl, imidazolyl substituted with phenyl or alkyl, or R^6 and R^7, or R^8 and R^9, together form a further fused ring.

(16) 2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-carboxylic acid derivatives (I) WO 93-21171 as shown below:



(I)

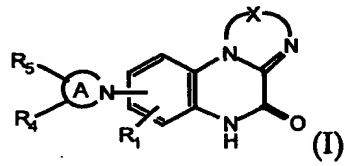
The present invention relates to the use of derivatives of the 2H-1,2,4-benzothiadiazin-1,1-dioxide-3-carboxylic acid of the above formula or the salts of such compound or of intermediates of such compound for the preparation of AMPA receptor antagonists and to new componds of the formula (I), their preparation and the medications in which they are found.

In the formula (I): R_1 is carboxy, alkoxycarbonyl, tetrazolyl, -CO-NH_2, -CO-NH-alk, -CO-N(alk)$_2$, -CO-NHOH, -CO-N(alk)OH, -CO-NH-O-R_5, -CO-N(alk)-OR_5 or a group that may be converted into a carboxyl moiety in vivo; R_2, R_3 and R_4 are the same or different and are selected from the group consisting of hydrogen, halogen or alkyl; R_5 is alkyl or phenylalkyl.

The term alk refers to an alkyl or alkylene group. Clearly, the compounds of the present invention include the tautomers of the compounds of the formula (I). The groups, convertible into carboxyl moieties in vivo, include -CO-R_6, in which R_6 is -O-alk-R_7, -O-alk-O-CO-alk, -O-alk-O-COOalk, -O-alk-O-CO-R_7, -O-alk-OH, -O-alk-O-alk, -O-alk-S-alk, -O-alk-O-R_7, -O-alk-S-R_7, -O-alk-COOH, -O-alk-COOalk, -O-alk-NR_8R_9, -NH-alk-O-CO-alk, -NH-alk-O-COOalk, -NH-alk-O-CO-R_7, -NH-alk-OH, -NH-alk-O-alk, -NH-alk-S-alk, -NH-alk-O-R_7, -NH-alk-S-R_7, -NH-alk-COOH, -NH-alk-COOalk, -NH-alk-NR_8R_9. In these definitions, R is alkyl or alkylene, R_7 phenyl, R_8 and R_9 are the same or different and are selected from the group consisting of hydrogen, alkyl, phenyl or phenylalkyl or form with the oxygen atom they are attached to a piperidinyl, morpholinyl or pyrrolidinyl ring. The halogen atoms are selected from the following: fluoride, chloride, bromide or iodide. Unless otherwise stated, in the above and below definitions, the alkyl, alkoxy and alkylene groups are a straight or branched alkyl chain having one to six carbon atom, and preferably one to four carbon atoms. The compounds of the formula (I) in which either R_2, R_3 and R_4 are hydrogen and R_1 is carboxy, alkoxycarbonyl, -CO-NH_2 or -CO-NH-alk, or R_4 a chloride or bromide atom, R_2 and R_3 are hydrogen and R_1 is carboxy, alkoxycarbonyl, -CO-NH_2 or -CO-NH-alk, or R_3 a chloride or bromide

atom, R_2 and R_4 are hydrogen and R_1 is carboxy, alkoxycarbonyl, -CO-NH_2 or -CO-NH-alk. The present invention include also other compounds of the formula (I), their salts or intermediates of their salts. In these compounds, R_1 is carboxy, alokoxycarbonyl, tetrazolyl, -CO-NH_2, -CO-NH-alk, -CO-N(alk)$_2$, -CO-NHOH, -CO-N(alk)OH, CO-NH-O-R_5, CO-N(alk)-OR_5 or -CO-R_6, in which R_6 is -O-alk-R_7, -O-alk-O-CO-alk, -O-alk-O-COOalk, -O-alk-O-CO-R_7, -O-alk-OH, -O-alk-O-alk, -O-alk-S-alk, -O-alk-O-R_7, -O-alk-S-R_7, -O-alk-COOH, -O-alk-COOalk, -O-alk-NR_8R_9, -NH-alk-O-CO-alk, -NH-alk-O-COOalk, -NH-alk-O-CO-R_7, -NH-alk-OH, -NH-alk-O-alk, -NH-alk-S-alk, -NH-alk-O-R_7, -NH-alk-S-R_7, -NH-alk-COOH, -NH-alk-COOalk, -NH-alk-NR_8R_9, R_2, R_3 and R_4 are the same or different and are selected from the group consisting of hydrogen, halogen or alkyl, R_5 is alkyl or phenylalkyl, R_7 is phenylalkyl, R_8 and R_9 are the same or different and are selected from the group consisting of hydrogen, alkyl, phenyl or phenylalkyl or form with the oxygen atom they are attached to a piperidinyl, morpholinyl or pyrrolidinyl ring. The term alk refers to an alkyl or alkylene group. The present invention does not include the compounds of the formula (I) in which either R_2, R_3 and R_4 are hydrogen and R_1 is carboxy, alkoxycarbonyl, -CO-NH_2 or -CO-NH-alk, or R_4 a chloride or bromide atom, R_2 and R_3 are hydrogen and R_1 is carboxy, alkoxycarbonyl, -CO-NH_2 or -CO-NH-alk, or R_3 a chloride or bromide atom, R_2 and R_4 are hydrogen and R_1 is carboxy, alkoxycarbonyl, -CO-NH_2 or -CO-NH-alk .

(17) Fused quinoxalinone derivatives (I) in WO 93-20077 as shown in below:

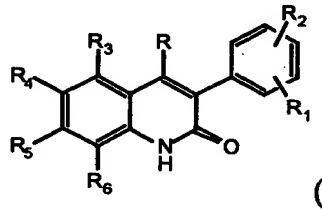


(I)

A fused quinoxalinone derivative represented by general formula(I), a tautomeric isomer thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing the same, which has a glutamate receptor antagonism and is useful as anti-ischemic and pshychotropic, wherein *a* represents a 5-membered

heterocyclic group containing two or three nitrogen atoms, R^1 represents nitro or trifluoromethyl, X represents (a), (b), (c) or (d), and R^2, R^3, R^4, R^5 and R^6 may be the same or different from one another and each represents hydrogen or lower alkyl which may be substituted by mono- or di(lower alkyl)amino.

(18) Quinolone derivatives (I) in WO 93-11115 as shown in below:

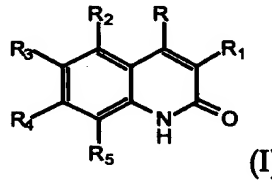


(I)

Compounds of formula I or a pharmaceutically acceptable salt thereof or a prodrug thereof: wherein R represents a hydrogen atom, an amino group, a carboxy or C_{2-6} alkoxycarbonyl group, or a group of formula -A-B-E, in which A represents a chemical bond, an oxygen or sulphur atom, or an -NH- group; B represents a carbonyl (C=O) or sulphonyl (SO_2) group, or a straight or branched alkylene chain containing from 1 to 6 carbon atoms; and E represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cyano, phenyl, tetrazolyl, methyloxadiazolyl, $-NR^aR^b$, $-COR^a$, $-C(=N.OR^a)R^b$, $-CO_2R^a$, $-CONR^aR^b$, $-CONR^a.OR^b$ or $-CH_2CO_2R^a$; R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, NR^aCOR^b, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; one of R^3, R^4, R^5 and R^6 represents hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^a$ or $-CONR^aR^b$, and the other three of R^3, R^4, R^5 and R^6 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, -

NR^aCOR^b, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$, and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

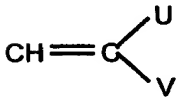
(19) Quinolone derivatives (I) in WO 93-10783 as shown below:



(I)

Compounds of formula I or a pharmaceutically acceptable salt thereof or a prodrug thereof wherein R represents a hydrogen atom, an amino group, a carboxy or C_{2-6} alkoxycarbonyl group, or a group of formula $-\alpha-\beta-\epsilon$, in which α represents a chemical bond, an oxygen or sulphur atom, or an -NH- group; β represents a carbonyl (C=0) or sulphonyl (SO_2) group, or a straight or branched alkylene chain containing from 1 to 6 carbon atoms; and ϵ represents C_{1-6} alkyl, C_{2-6} alkenyl, phenyl, $-NR^aR^b$, $-CO_2R^a$ or $-CH_2CO_2R^a$; R^1 is a group of part formula (i) or (ii):

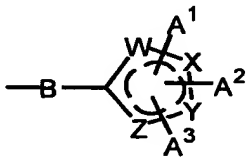
$-(CH=CH)_n-T$ (i)



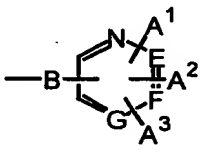
(ii)

wherein U and V independently represent cyano, carboxy, $-COR^6$, $-CO_2R^6$, $-CO.SR^6$, -CONHOH or $-CONHNH_2$; n is zero or 1, preferably zero; T represents cyano, carboxy, $-COR^6$, $-CO_2R^6$, $-CO.SR^6$, -CONHOH, - $CONHNH_2$ or a group of formula in which the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; B represents a bond or a carbonyl group (C=0); W, X, Y and Z independently represent oxygen, sulphur, nitrogen or carbon,

provided that no more than one of W, X, Y and Z represents oxygen or sulphur and at least one of W, X, Y and Z is other than carbon; one of E, F and G represents nitrogen or carbon and the remainder represent carbon; A^1, A^2 and A^3 represent one, two or three substituents not exceeding the maximum number permissible by the disposition of heteroatoms in the five- or six-membered ring, which substituents are independently selected from hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or A^1 and A^2 or A^2 and A^3 together represent the residue of an aromatic or heteroaromatic ring;

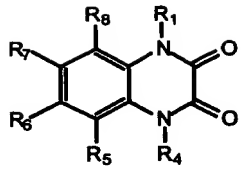


or



one of R^2, R^3, R^4 and R^5 represents hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$, and the other three of R^2, R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^2 and R^3, R^3 and R^4 or R^4 and R^5 together represent the residue of an aromatic or heteroaromatic ring; R^6 represents hydrocarbon or a heterocyclic group; and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

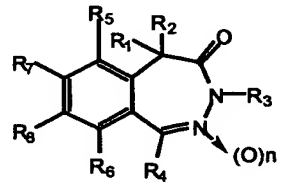
(20) Quinoxaline derivatives (I) in WO 93-08173 as shown below:



(I)

Quinoxaline derivates of the formula (I), in which R^1 is C_{1-12}-alkyl substituted by R^2, C_{2-12}-alkenyl substituted by R^2, C_{2-12}-alkinyl substituted by R^2, C_{3-7}-cycloalkyl substituted by R^2, $-(CH_2)_n-C_{6-12}$-aryl substituted by R^2 in the aryl or alkyl residue or $-(CH_2)_n$-hetaryl substituted by R^2 in the hetaryl or alkyl residue; R^4 is hydrogen, C_{1-12}-alkyl substituted by R^2, C_{2-12}-alkenyl substituted by R^2, C_{2-12}-alkinyl substituted by R^2, $(CH_2)_n-C_{6-12}$-aryl substituted by R^2 in the aryl or alkyl residue, or $-(CH_2)_n$-hetaryl substituted by R^2 in the hetaryl or alkyl residue; R^5, R^6, R^7 and R^8 are the same or different and represent hydrogen, halogen, nitro, NR^9R^{10}, $NHCOR^{11}$, SO_2R^{12}, C_{3-7}-cycloalkyloxy, COR^{13}, cyano, CF_3, C_{1-6}-alkyl, C_{1-4}-alkoxy or imidazole possibly substituted by cyano, C_{1-4}-alkyl or $-COO-C_{1-6}$ -alkyl or R^5 and R^6 or R^7 and R^8 represent a condensated benzene ring, and R^2 stands for $-CO-R^3$, or -PO-XY and is present once or twice in the same or a different form.

(21) Substituted 2,3-benzodiazepin-4-one (I) in WO 97-34878 as shown below:

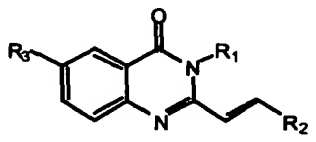


(I)

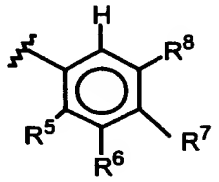
Substituted 2,3-benzodiazepin-4-one represented by formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein: R_1 and R_2 are independently hydrogen, alkyl, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl or thioalkyl; or R_1 and R_2 are taken together to form a carbocycle or heterocycle; R_3 is hydrogen, alkyl, haloalkyl, aryl,

fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, COR, CO_2R and $CONR_xR_y$, wherein R, R_x and R_y are independently hydrogen, alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, or aminoalkyl; or R_x and R_y are taken together to form a carbocycle or heterocycle; R_4 is substituted or unsubstituted aryl, fused aryl, a carbocyclic group, a heterocyclic group, or a heteroaryl group; R_5 and R_6 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, carboxy, carbonylamido or alkylthiol; R_7 and R_8 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or R_7 and R_8 are taken together to form a carbocycle or heterocycle, for example, $-OCH_2O$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-OCH_2CH_2O-$, $-CH_2N(R)CH_2-$, $-CH_2CH_2N(R)CH_2-$, $-CH_2N(R)CH_2CH_2-$, -N(Me)-C(O)-O- and -N=C-C=N-, wherein R is a defined above; and n is 0 or 1.

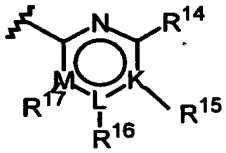
(22) 2,3-Disubstituted-4(3H)-quinazolinone in WO97-43276 as shown below:



Bicyclic compounds of the formula wherein R^1 is optionally substituted phenyl of the formula Ph^1 or heteroaryl wherein said heteroaryl is selected from the group consisting of pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, wherein said heteroaryl may optionally be substituted on any of the ring carbon atoms capable of forming an additional bond, up to a maximum of three substituents per ring, with a substituent selected from hydrogen, (C_1-C_6)alkyl, halogen, trifluoromethyl, amino-(CH_2)$_n$-, (C_1-C_6)alkylamino-(CH_2)$_n$-, di(C_1-C_6)alkyl-amino-(CH_2)$_n$-, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl-O-(C_1-C_6)alkyl-, -CN, (C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-, (C_1-C_6)alkyl-O-C-O-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C-O-, hydroxy, H-C(=0)-, (C_1-C_6)alkyl-C(=0)-(CH_2)$_n$-, HO-C(=0)-(CH_2)$_n$-, (C_1-C_6)alkyl-O-C(=0)-(CH_2)$_n$-, NH_2-C(=0)-(CH_2)$_n$-, (C_1-C_6)alkyl-NH-C(=0)-(CH_2)$_n$-, and di(C_1-C_6)alkyl-NH-C(=0)-(CH_2)$_n$-,wherein said Ph^1 is a group of the formula

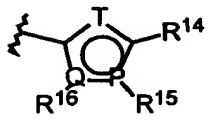


R^2 is phenyl of the formula Ph^2 or a five or six membered heterocycle, wherein said 6-membered heterocycle has the formula

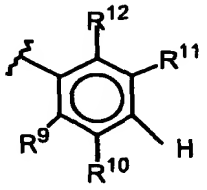


wherein "N" is nitrogen; wherein said ring positions "K", "L" and "M" may be independently selected from carbon or nitrogen, with the proviso that i) only one of "K, "L" or "M" can be nitrogen and ii) when "K", "L" or "M" is nitrogen then its

respective R^{15}, R^{16} or R^{17} is absent; wherein said five membered heterocycle has the formula



wherein said "T" is -CH-, N, NH, O or S; wherein said ring positions "P" and "Q" may be independently selected from carbon, nitrogen, oxygen or sulfur; with the proviso that only one of "P", "Q" or "T" can be oxygen or sulfur and at least one of "P", "Q" or "T" must be a heteroatom; wherein said Ph^2 is a group of the formula

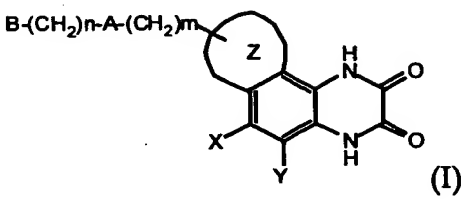


R^3 is hydrogen, halo, -CN, $-NO_2$, CF_3, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy; R^5 is hydrogen, $(C_1\text{-}C_6)$alkyl, halo, CF_3, $(C_1\text{-}C_6)$alkoxy or $(C_1\text{-}C_6)$alkylthiol; R^6 is hydrogen or halo; R^7 is hydrogen or halo; R^8 is hydrogen or halo; R^9 is hydrogen, halo, CF_3, $(C_1\text{-}C_6)$alkyl optionally substituted with one to three halogen atoms, $(C_1\text{-}C_6)$alkoxy optionally substituted with one to three halogen atoms, $(C_1\text{-}C_6)$alkylthiol, amino-$(CH_2)_s$-, $(C_1\text{-}C_6)$alkyl-NH-$(CH_2)_s$-, di$(C_1\text{-}C_6)$alkyl-N-$(CH_2)_s$-, $(C_3\text{-}C_7)$cycloalkyl-NH-$(CH_2)_s$-, H_2N-(C=0)-$(CH_2)_s$-, $(C_1\text{-}C_6)$alkyl-HN-(C=0)-$(CH_2)_s$-, di$(C_1\text{-}C_6)$alkyl-N-(C=0)-$(CH_2)_s$-, $(C_3\text{-}C_7)$cycloalkyl-NH-$(CH_2)_s$-, R^{13}0-$(CH_2)_s$-, R^{13}0-(C=0)-$(CH_2)_s$, H(0=C)-NH-$(CH_2)_s$-, $(C_1\text{-}C_6)$alkyl-(0=C)-n-$(CH_2)_s$-, H(0=C)-$(CH_2)_s$-, $(C_1\text{-}C_6)$alkyl-(C=0)-, hydroxy, hydroxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl-, and -CN; R^{10} and R^{14} are selected, independently, from hydrogen, halo, CF_3, $(C_1\text{-}C_6)$alkyl optionally substituted with one to three halogen atoms, $(C_1\text{-}C_6)$alkoxy optionally substituted with one to three halogen atoms, $(C_1\text{-}C_6)$alkylthiol, amino-$(CH_2)_p$-, $(C_1$-

C_6)alkyl-NH-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-$(CH_2)_p$-, amino-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, (C_1-C_6)alkyl-NH-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-N-$(CH_2)_p$-, H_2N-(C=0)-$(CH_2)_p$-, H_2N-(C=0)-$(CH_2)_p$-, (C_1-C_6)alkyl-HN-(C=0)-$CH_2)_p$-, (C_3-C_7)cycloalkyl-NY-(C=0)-$(CH_2)_p$-, R^{13}0-(C=0)-$(CH_2)_p$-, H(O=C)-O-, H(O=C)-O-(C_1-C_6)alkyl-, H(0=C)-NH-$(CH_2)_p$-, (C_1-C_6)alkyl-(0=C)-NH-$(CH_2)_p$-, -CHO, H-C(C=0)-$(CH_2)_p$-, (C_1-C_6)alkyl-(C=0)-$(CH_2)_p$-, (C_1-C_6)alkyl-(0=C)-N-$(CH_2)_p$-, H(0=C)-N-$(CH_2)_p$-, HO-(C_1-C_6)Alkyl-N-$(CH_2)_p$-, (C_1-C_6)alkyl-(C=0)-O-NH-$(CH_2)_p$-, amino-(C_1-C_6)alkyll-(C=0)-O$(CH_2)_p$, (C_1-C_6)alkyl, (C_1-C_6)alkyl-NH-(C_1-C_6)alkyl-(C=0)-O-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-(C=0)-0-$(CH_2)_p$-, amino-(C_1-C_6)alkyl-O-(C=0)-$(CH_2)_p$, (C_1-C_6)alkyl-NH-(C_1-C_6)alkyl-O-(C=O)-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-O-(C=0)-(CH_2)p-, hydroxy, hydroxy-(C_1-C_6)alkyl-, hydroxy-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, (C_1-C_6)alkyl-O-(C_1-C_6)alkyl-, -CN, piperidine-$(CH_2)_p$-, pyrrolidine-$(CH_2)_p$-, and 3-pyrroline-$(CH_2)_p$-, wherein said piperidine, pyrrolidine and 3-pyrroline of said piperidine-$(CH_2)_p$-, pyrrolidine-$(CH_2)_p$- and 3-pyrroline-$(CH_2)_p$- moieties may optionally be substituted on any of the ring carbon atoms capable of supporting and additional bond, preferably zero to two substitutents, with a substituent independently selected from halo, CF_3, (C_1-C_6)alkyl optionally substituted with one to three halogen atoms, (C_1-C_6)alkoxy optionally substituted with one to three halogen atoms, (C_1-C_6)alkylthiol, amino-$(CH_2)_p$-, (C_1-C_6)alkyl-NH-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-$(CH_2)_p$-, (C_3-C_7)cycloalkyl-NH-$(CH_2)_p$-, amino-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, (C_1-C_6)alkyl-NH-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, (C_1-C_6)alkyl-O-(C_1-C_6)alkyl-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-N-$(CH_2)_p$-, H_2N-(C=0)-$(CH_2)_p$-, (C_1-C_6)alkyl-HN-(C=0)-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C=0)-$(CH_2)_p$, C_3-C_7)cycloalkyl-NH-(C=0)-$(CH_2)_p$-,R^{13}0-$(CH_2)_p$-, R^{13}0-(C=0)-$(CH_2)_p$-, H(0=C)-0-, H(0=C)-0-(C_1-C_6)alkyl-, H(0=C)-NH-$(CH_2)_p$-, (C_1-C_6)alkyl-(0=C)-NH-$(CH_2)_p$-, -CHO, H-(C=0)-$(CH_2)_p$-, (C_1-C_6)alkyl-(C=0)-, (C_1-C_6)alkyl-(0=C)-N-$(CH_2)_p$-, H(0=C)-n-$(CH_2)_p$-, HO-(C_1-C_6)alkyl-N-$(CH_2)_p$-, (C_1-C_6)alkyl-(C=0)-0-NH-$(CH_2)_p$-, amino-(C_1-C_6)alkyl-(C=0)-0-$(CH_2)_p$-, (C_1-C_6)alkyl-NH-(C_1-C_6)alkyl-(C=0)-0-$(CH_2)_p$-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-(C=0)-0-$(CH_2)_p$-,

hydroxy, hydroxy-(C_1-C_6)alkyl-, hydroxy-(C_1-C_6)alkyl-NH-$(CH_2)_p$-, and -CN; R^{11} is hydrogen or halo; R^{12} is hydrogen, -CN or halo; R^{13} is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-(C=0)-, (C_1-C_6)alkyl-O-(C=0)-, (C_1-C_6)alkyl-NH-(C=0)-, or di(C_1-C_6)alkyl-N-(C=0)-; R^{15} is hydrogen, -CN, (C_1-C_6)alkyl halo, CF_3, -CHO or (C_1-C_6)alkoxy; R^{16} is hydrogen, -CN, (C_1-C_6)alkyl, halo, CF_3, -CHO or (C_1-C_6)alkoxy; R^{17} is hydrogen, -CN, (C_1-C_6)alkyl, amino-(C_1-C_6)alkyl-, (C_1-C_6)alkyl-NH-(C_1-C_6)alkyl-, di(C_1-C_6)alkyl-N-(C_1-C_6)alkyl-, halo, CF_3, -CHO or (C_1-C_6)alkoxy; n is an integer from zero to 3; each p is independently an integer from zero to 3; s is an integer from zero to 4; wherein the dashed bond represented an optional double bond; with the proviso that: i) when R^9 is hydrogen, one of R^{11} and R^{12} is other than hydrogen; ii) when R^1 is unsubstituted phenyl and R^3 is hydrogen then (a) R^2 can not be unsubstituted phenyl, thienyl or furyl or (b) R^9 can not be CI or hydroxy when R^{10} and R^{11} are hydrogen, or (c) R^{10} or R^{11} can not be chloro when R^9 and R^{12} are hydrogen; iii) when R^3 is hydrogen; R^6, R^7 and R^8 are hydrogen; and R^5 is chloro or methyl, then (a) R^2 can not be unsubstituted phenyl, thienyl or furyl or (b) R^{10} or R^{11} can not be chloro or (c) R^9 or R^{12} can not be hydroxy, methyl or methoxy; iv) when R^3 is hydrogen or chloro; R^5 is methyl; R^6, R^7 and R^8 are hydrogen; and K, L and M equal carbon, then (a) one of R^{14} through R^{17} must be other than hydrogen or (b) R^{17} must be other than hydrogen or methyl; v) when R^1 is unsubstituted pyridin-2-yl and R^3 is hydrogen, bromo or iodo then R^2 can not be unsubstituted phenyl; vi) when R^7 is chloro; R^5, R^6, and R^8 are hydrogen; and R^3 is hydrogen, then (a) R^2 can not be unsubstituted phenyl, pyridyl, thienyl or furyl or (b) R^9 or R^{12} can not be hydroxy when R^{10} and R^{11} are hydrogen; vii) when R^2 is unsubstituted phenyl, R^6, R^7 and R^8 are hydrogen, and R^3 is hydrogen, then R^5 can not be -CO_2H; viii) when R^2 is unsubstituted pyridin-2-yl, R^5 and R^7 are hydrogen, then R^6 or R^8 must be other than chloro; ix) when R^2 is unsubstituted phenyl, R^3 is hydrogen, and R^5 and R^7 are hydrogen, then one of R^6 or R^8 must be other than chloro; and the pharmaceutically acceptable salts of such compounds.

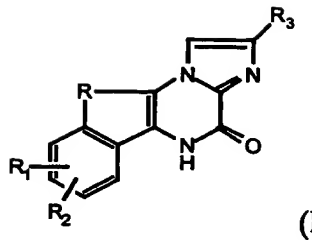
(23) Fused cycloalkyl quinoxalinedione (I) in WO 98-05651 as shown below:



(I)

Compounds represented by the formula (I) or pharmaceutically acceptable salts thereof wherein Z is a carbocyclic fused ring having 5 to 7 carbon atoms; X and Y are independently hydrogen, halogen, nitro, cyano, $-CF_3$, -COOH, $-CONR^1R^2$, $-COR^3$, $-SO_2R^3$, imidazolyl or imidazolidinyl, wherein R^1 and R^2 are independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl, aralkyl or join together to form a heterocyclic ring and wherein R^3 is alkyl, haloalkyl, cycloalkyl, aryl or aralkyl; A is a bond, O, S, NR^4, NR^4CO, NR^4CS, $CONR^4$, $CSNR^4$, CO or CS wherein R^4 is hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl, aralkyl or when n = 0 then R^4 and B may join together to form a heterocyclic ring; B is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, R^5, CN, COR^5, $PO_3R^5_2$, SO_2R^5, or heterocyclic, wherein R^5 is hydroxy, alkoxy, aralkoxy, aryloxy or NR^1R^2; and m and n are independently 0, 1, and 2, provided that (i) m is not 0 when A is 0, CN, tetrazole or CO, except when A is CO and B is a heterocyclic or when A is 0 and B is COR^5, $PO_3R^5_2$ or SO_2R^5; (ii) m is not 0 or 1 when A is NR^4, except when B is COR^5, $PO_3R^5_2$ or SO_2R^5; and (iii) n is not) when A is 0, S, NR^4, $CONR^4$ and B is NR^1R^2, CN, COR^5, or $PO_3R^5_2$.

(24) Imidazo[1,2-a]indeno[1,2-e]pyrazine-2-carboxylic acid derivatives (I) and their salts as shown in WO 96-02544 A1 as shown below:



(I)

Imidazo[1,2-a]indeno[1,2-e]pyrazine-2-carboxylic acid derivatives having general formula (I) wherein R is N-alk, $C(R_4)R_5$, CH-R_6 or C=R_7, R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, amino, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl, SO_3H, hydroxy, polyfluoralkoxy, carboxy, alkylcarbonyl, -NH-CO-$NR_{11}R_{12}$, -N(alk)-CO-$NR_{11}R_{12}$, -N(alk-Ar)-CO-$NR_{11}R_{12}$, -NH-CS-$NR_{11}R_{12}$, -N(alk)-CS-$NR_{11}R_{12}$, -NH-CO-NR_{11}, -NH-CS-R_{24}, -NH-C(=NR_{27})-$NR_{10}R_{12}$, -N(alk)-C(=NR_{27})-$NR_{10}R_{12}$,, -CO-$NR_{10}R_{12}$, -NH-SO_2-$NR_{10}R_{12}$, N(alk)-SO_2-$NR_{10}R_{12}$, -NH-SO_2-CF_3, -NH-SO_2-alk, -$NR_{10}R_{13}$, $S(O)_m$-alk-Ar, -SO_2-$NR_{10}R_{12}$, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R_3 is carboxy, alkoxycarbonyl or carboxamide, R_4 is alkyl, -alk-Het or phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, R_5 is an alkyl group (the term C_1-C_{11} alkyl represents a straight or branched alkyl chain having one to eleven carbon atoms), -alk-Het, NR_8R_9, -NH-CHO, -NH-$COOR_{17}$, -NH-SO_2R_{24}, -$COOR_{10}$, -alk-$COOR_{10}$, -alk-$CONR_{10}R_{18}$, -alk-$NR_{10}R_{18}$, -alk-OH, -alk-CN, phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-$COOR_{10}$, -NH-CO-alk-$NR_{10}R_{18}$, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy,

nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, pyrrol-1yl possibly substituted by -$COOR_{10}$, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-NH-Het, -NH-CO-NH-alk-Het, -NH-CO-NH-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-COalk, -NH-COcycloalkyl, -NH-CO-NH-alk or -NH-CO-NH_2, or R_4 and R_5, together with the carbon atom they attached to, are a cycloalkyl group, R_6 is hydrogen, hydroxy, alkyl (the term C_1-C_{11} alkyl represents a straight or branched alkyl chain having one to eleven carbon atoms), -alk-OH, -$NR_{14}R_{15}$, -alk-$NR_{14}R_{15}$,, alk-Het, -NH-CHO, -COOalk, -alk-$COOR_{10}$, -alk-CO-$NR_{10}R_{21}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -R_{16}-$COOR_{10}$, -CO-$COOR_{10}$ or pyrrol-1yl which may be substituted by -$COOR_{10}$, or 2-oxo-2,5-dihydropyrrol-1-yl, R_7 is oxygen or NOH, NO-alk-$COOR_{10}$, NO-alk, CHR_{19}, NR_{10}, C($COOR_{10}$)R_{20} or C($CONR_{10}R_{21}$)R_{20}, R_8 is hydrogen, alkyl, -alk-$COOR_{10}$, -alk-$NR_{10}R_{21}$, -alk-Het or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$ and -alk-$COOR_{10}$, R_9 is hydrogen or alkyl, R_{10} is hydrogen or alkyl, R_{11} is hydrogen, alkyl (the term C_1-C_9 alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), -alk-$COOR_{10}$, alk-Het, -alk-$NR_{12}R_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano, and -alk-$COOR_{10}$ or Het, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano, and -alk-$COOR_{10}$ or Het, R_{12} is hydrogen or alkyl, R_{13} is alkyl, Het or alkoxycarbonyl, R_{14} and R_{15} are the same or different and are each an alkyl group or R_{14} is hydrogen and R_{15} is hydrogen, alkyl, -COR_{22}, -CSR_{23} or SO_2R_{24}, R_{16} is a -CHOH or -CH(OH)-

alk(C_1-C_5) chain, R_{17} is alkyl or phenylalkyl, R_{18} is hydrogen or alkyl, R_{19} is hydroxy, alkyl, alk-Het, -$NR_{25}R_{26}$, -alk-$COOR_{10}$, -Het , phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, or , phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano, and -alk-$COOR_{10}$, R_{20} is hydrogen or alkyl, R_{21} is hydrogen or alkyl, R_{22} is alkyl, cycloalkyl, -COOalk, -alk-$COOR_{10}$, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano and -alk-$COOR_{10}$,-alk-$NR_{10}R_{12}$, -NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, -Het, -alk-Het, -OR_{17}, -NH-alk-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, -$COOR_{10}$, cyano and -alk-$COOR_{10}$, NH-alk-Het, -NH-alk, -NH_2 or -NH-Het, R_{23} is -NH-alk, -NH-Ar, -NH-Het or -NH_2, R_{24} is alkyl or phenyl, R_{25} and R_{26} are the same or different and are each alkyl or cycloalkyl, R_{27} is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene group. The term alk' refers to an alkyl group, m = 0,1 or 2. The term Ar refers to a phenyl group. The term Het refers to a heterocycle which is mono or poly saturated or unsaturated with four to nine carbon atoms and one or more heteroatom (O, S, N) which may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl.

Unless otherwise stated, in the above and below definitions, the alkyl or alkylene groups are a straight or branched alkyl chain having one to six carbon atom, the acyl groups have two to four carbon atoms, the cycloalkyl groups have

three to six carbon atoms and the halogen are of the following: fluoride, chloride, bromide, or iodide.

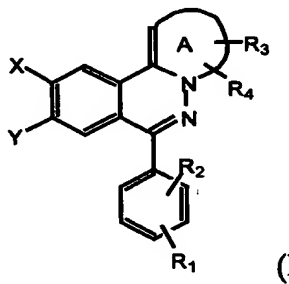
Preferably, Het is one of the following rings: pyrrolyl, pyridyl, pyrimidinyl, imidazolinyl, thiazolyl, oxazolinyl, thiazolinyl, pyrazinyl, tetrazolyl, triazolyl. Each of these rings can possibly be substituted by one or more of the following: alkyl, phenyl or phenylalkyl. The preferred substitutants are methyl, phenyl or benzyl.

The compounds of the formula (I) in which R_7 is NO-alk, $C(COOR_{10})R_{20}$, $C(CONR_{10}R_{21})R_{20}$ or CHR_{19} can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

The compounds of the formula (I), in which R is CH-R_6 and R_6 is -CO-$COOR_{10}$, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures.

The compounds of the present invention include the eniantomers and diastereoisomers of the compounds of the formula (I), in which R is $C(R_4)R_5$ or CH-R_6.

(25) Phthalazine derivatives (I) in DE 196 17 862 A1 as shown below:

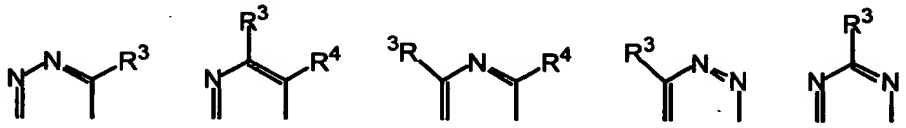


(I)

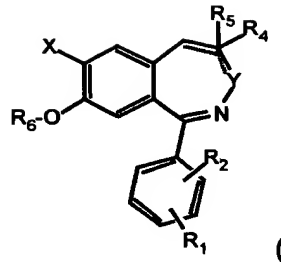
Phthalazine derivatives of the formula I wherein R^1 and R^2 are identical or different and hydrogen, C_1-C_6-alkyl, nitro, halogen, the group -NR^8R^9, -O-C_1-4-alkyl or CF_3; R^3 and R^4 are identical or different and hydrogen, an eventually substituted C_1-C_6-alkyl-, aryl- or hetaryl residue or C_{3-7}-cycloalkyl; R^8 and R^9 are identical or different and hydrogen, C_1-C_6-alkyl or the group -CO-C_{1-6}-alkyl, X hydrogen; Y C_{1-6}-alkoxy or X and Y together -O-$(CH_2)_n$-O-; n 1, 2 or 3 mean and A forms together with

nitrogen a fifemembered heterocycle, which can contain 1-3 nitrogen atoms, as well as its isomers and pharmaceutically acceptable salts thereof.

Under alkyl one has to understand a linear or branched alkyl residue as for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sek. butyl, pentyl, isopentyl or hexyl, which can be substituted by C_1-C_6-alkoxy, halogen or C_1-C_6-alkonyl. If there is a halogenated alkyl residue present, then it can be multiple halogenated or perhalogenated such as CF_3. Under halogen one has to understand fluoride, chloride, bromide and iodide. The aryl- and hetaryl residue R^3 and R^4 can be single or multiple substituted with halogen, C_{1-4}-alkoxy or C_{1-4}-alkyl. The alyl residue can contain 6-10 carbon atoms whereby phenyl is preferred. One might mention as a hetaryl residue for example pyridinyl. With cycloalkyl one means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, respectively, particularly C_{3-5}-cycloalkyl. Suitable as alkanoyl residues are alphatic carbonic acid residues such as formyl, acetyl, propionyl, butanoyl,caproyl, valeroyl, trimethylacetyl and others. If A together with the nitrogen atom forms a 5-membered heterocycle, then is in position 4 an exocyclic double bond. Preferred are heteroaromatics with 1-3 nitrogen atoms, whereby for example A has the following meaning:



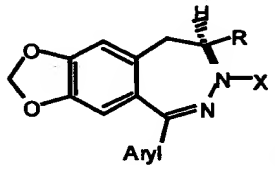
(26) 2,3-Benzodiazepine derivatives (I) in DE 196 04 920 A1 as shown below:



(I)

2,3-Benzodiazepine derivatives having general formula (I) wherein X is hydrogen or halogen, Y -NR^3-or-N=, R^1 and R^2 are identical or different and hydrogen, C_1-C_6-alkyl, nitro, halogen, the group -NR^8R^9, -O-C_{1-4}-alkyl or -CF_3, R^3 is hydrogen, the group -CO-R^{10}, C_{1-6}-alkyl or C_{3-7}-cycloalkyl; R^4 eventually substituted C_1-C_6-alkyl; R^5 hydrogen or R^4 and R^5 together oxygen; R^6 C_{1-4}-alkyl; R^8 and R^9 are identical or different and hydrogen, C_1-C_6-alkyl or -CO-C_{1-6}-alkyl; R^{10} hydrogen, eventually substituted C_1-C_6-alkyl, eventually substituted C_{6-10}-aryl, the group -$NR^{11}R^{12}$, -O-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl or -O-C_{3-7}-cycloalkyl; R^{11} and R^{12} are identical or different and hydrogen, eventually substituted C_1-C_6-alkyl or eventually substituted C_{6-10}-aryl and -C...C... a double bond or single bond means as well as their isomers and pharmaceutically acceptable salts thereof.

(27) Dihydro-2,3-benzodiazepine derivatives (I) in WO 96-06606 as shown below:

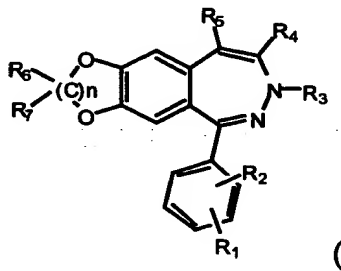


(I)

Dihydro-2,3-benzodiazepine derivatives having general formula (I) wherein R is hydrogen or C_1-C_{10} alkyl; X is an aromatic moiety selected from phenyl, thienyl, furyl, pyridyl, imidazolyl, benzimidazolyl, benzothiazolyl and phthalazinyl which is unsubstituted or substituted with one or more moieties chosen from the group consisting of halogen, hydroxy, cyano, nitro, C_1-C_6 alkyl, , C_3-C_6 cycloalkyl, C_1-C_4

alkoxy, carboxy, C_1-C_6 alkoxycarbonyl, acetyl, formyl, carboxymethyl, hydroxymethyl, amino, aminomethyl, methylenedioxy and trifluoromethyl; and "Aryl" represents p-nitrophenyl, p-aminophenyl or p-(protected amino) phenyl; or a pharmaceutically acceptable salt thereof.

(28) 3-Substituted 3H-2,3-benzodiazepine derivatives (I) in WO 96-04283 A1 as shown below:



(I)

3-Substituted 3H-2,3-benzodiazepine derivatives of general formula (I) wherein R^1 and R^2 are identical or different and hydrogen, C_1-C_6-alkyl, nitro, halogen, the group $-NR^8R^9$, $-O-C_{1-4}$-alkyl or CF_3; R^3 the group

$$-C(=O)-R^{10}$$

;

R^4 eventually substituted C_1-C_6-alkyl; R^5 hydrogen or eventually substituted C_1-C_6-alkyl; R^6 and R^7 are identical or different and hydrogen, eventually substituted C_1-C_6-alkyl or eventually substituted aryl; R^8 and R^9 are identical or different and hydrogen, C_1-C_6-alkyl or the group

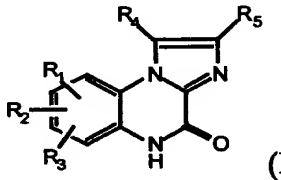
$$-C(=O)-R^{13}$$

;

R^{10} hydrogen, eventually substituted C_1-C_6-alkyl, eventually substituted aryl, the group $-NR^{11}R^{12}$, $-O-C_{1-6}$-alkyl, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl or $-O-C_{3-7}$-cycloalkyl; R^{11}

and R^{12} are identical or different and hydrogen, eventually substituted C_1-C_6-alkyl or eventually substituted aryl; R^{13} C_1-C_6-alkyl and n stands for 1, 2 or 3; means as well as their isomers and pharmaceutically acceptable salts thereof.

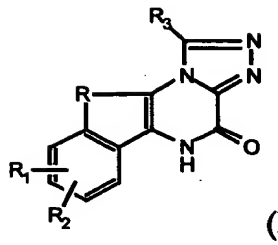
(29) Heterocyclic compounds (I) in WO 95-21842 as shown in below:



(I)

Imidazol[1,2-a]quinoxalinone derivatives of general formula (I) wherein R^1, R^2, R^3 are the same or independently are H, alkyl, alkoxy, halogen, NO_2, NH_2, CF_3, CN, SO_2CH_3, SO_2CF_3, $SO_2NR'R''$ or a 5- or 6- membered N- containing heterocyclic ring, optionally substituted, and R', R'' are independently H or alkyl; and R^4 is H or CH_2- R^6; and R^6 is H, halogen, POR'''R'''', NR^7R^8 or a 5- or 6-membered N-containing heterocyclic ring optionally substituted, and R''', R'''' are independently hydroxy or alkoxy; and R^7, R^8 are the same or independently are H, (a) or alkyl optionally substituted; and n is 1, 2, or 3; (b) CH_2OH, CHNOH, CN, (c) or (d) and R^9 is OH, alkoxy, H or $NR^{10}R^{11}$; and R^{10}, R^{11} are the same or independently are H, NH_2 or OH; and X is O or S; and Y is O, S or NH_2, and pharmaceutically acceptable salts thereof.

(30) 1,2,4-Triazolo[4,3-a]pyrazine-4-one derivatives and their salts in WO 95-26351 as shown below:



(I)

1,2,4-Triazolo[4,3-a]pyrazine-4-one derivatives having general formula (I) wherein R is N-alk, $C(R_4)R_5$, CH-R_6 or C=R_7. R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen or halogen atoms or of alkyl, alkoxy, amino, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl, SO_3H, hydroxy, polyfluoralkoxy, carboxy, alkoxycarbonyl, -NH-CO-$NR_{11}R_{12}$, -N(alk)-CO-$NR_{11}R_{12}$, -N(alk-Ar)-CO-$NR_{11}R_{12}$, -NH-CS-$NR_{11}R_{12}$, -N(alk)-CS-$NR_{11}R_{12}$, -NH-CO-R_{11}, -NH-CS-R_{24}, -NH-C(=NR_{27})-$NR_{10}R_{12}$, -N(alk)- C(=NR_{27})-$NR_{10}R_{12}$, -Co-$NR_{10}R_{12}$, -NH-SO_2-$NR_{10}R_{12}$, N(alk)-SO_2-$NR_{10}R_{12}$, -NH-SO_2-CF_3, -NH-SO_2-alk, -$NR_{10}R_{13}$, $S(O)_m$-alk-Ar, -SO_2-$NR_{10}R_{12}$, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R_3 is hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, phenylalkyl, phenyl, Het or amino, R_4 is alkyl, -alk-Het, or phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, R_5 is an alkyl group (the term C_1-C_{10} alkyl represents a straight or branched alkyl chain having one to ten carbon atoms), -alk-Het, -NR_8R_9, -NH-CHO, -NH-$COOR_{17}$, -NH-SO_2-R_{24}, -$COOR_{10}$, -alk-$COOR_{10}$, -alk-$CONR_{10}R_{18}$, -alk-$NR_{10}R_{18}$, -alk-OH, -alk-CN, phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-$COOR_{10}$, -NH-CO-alk-$NR_{10}R_{18}$, -NH-CO-alk-Ar in which Ar is substituted by one or more of the

following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, pyrrolyl-1which may be substituted by -$COOR_{10}$, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-NH-Het, -NH-CO-NH-alk-Het, -NH-CO-NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-COalk, -NH-COcycloalkyl, -NH-CO-NH-alk or -NH-CO-NH_2, or R_4 and R_5, together with the carbon atom they attached to, are a cycloalkyl group, R_6 is hydrogen, hydroxy, alkyl (the term C_1-C_{10} alkyl represents a straight or branched alkyl chain having one to ten carbon atoms), -alk-OH, -$NR_{14}R_{15}$, -alk-$NR_{14}R_{15}$, -alk-Het, -NH-CHO, -COO-alk, -alk -$COOR_{10}$, -alk-CO-$NR_{10}R_{18}$, -phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, R_{16}-$COOR_{10}$, -CO-$COOR_{10}$ or pyrrolyl-1 possibly substituted by -$COOR_{10}$.

R_7 is oxygen, or NOH, NO-alk-$COOR_{10}$, NO-alk, CHR_{19}, NR_{10}, C($COOR_{10}$) or C($CONR_{10}R_{21}$)R_{20}, R_8 is hydrogen, alkyl, -alk-$COOR_{10}$, -alk-$NR_{10}R_{21}$, -alk-Het or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, R_9 is hydrogen or alkyl, R_{10} is hydrogen or alkyl, R_{11} is hydrogen, alkyl, (the term C_1-C_9 alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), alkoxy, -alk-$COOR_{10}$, -alk-Het, -alk-$NR_{12}R_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano, and -alk-$COOR_{10}$, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano and -alk-$COOR_{10}$ or-Het, R_{12} is hydrogen or alkyl, R_{13} is alkyl, Het or alkoxycarbonyl, R_{14} and R_{15} are the same or different and are each an alkyl moiety, or R_{14} is hydrogen and R_{15} is hydrogen, alkyl, -COR_{22}, -

CSR_{23} or $-SO_2R_{24}$, R_{16} is a -CHOH- chain or $-CH(OH)-alk(C_1-C_5)$, R_{17} is alkyl or phenylalkyl, R_{18} is hydrogen or alkyl, R_{19} is hydroxy, alkyl, -alk-Het, $-NR_{25}R_{26}$, $-alk-COOR_{10}$, -Het, -phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano, and $-alk-COOR_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano and $-alk-COOR_{10}$, R_{20} is hydrogen or alkyl, R_{21} is hydrogen or alkyl, R_{22} is alkyl, cycloalkyl, -COOalk, $-alk-COOR_{10}$, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano and $-alk-COOR_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano and $-alk-COOR_{10}$, $-alk-NR_{10}R_{12}$, -NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano and $-alk-COOR_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano and $-alk-COOR_{10}$, -Het, -alk-Het, $-OR_{17}$, -NH-alk-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, $-alk-NH_2$, $-COOR_{10}$, cyano and $-alk-COOR_{10}$, -NH-alk-Het, -NH-alk, $-NH_2$ or -NH-Het, R_{23} is -NH-alk, -NH-Ar, -NH-Het or $-NH_2$, R_{24} is alkyl or phenyl, R_{25} and R_{26} are the same or different and are each alkyl or cycloalkyl, R_{27} is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene moiety. The term alk' refers to an alkyl moiety. m = 0,1 or 2. The term Ar refers to a phenyl moiety. The term Het refers to a heterocycle which is mono- or poly- saturated or unsaturated with one to nine carbon atoms and one or more heteroatom (O, S, N) which may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl.

Unless otherwise stated, in the above and below definitions, the alkyl, alkylene or alkoxy moieties are a straight or branched chain having one to six

carbon atom, the acyl moieties have two to four carbon atoms, the cycloalkyl moieties have three to six carbon atoms and the halogen atoms are selected from the following: fluoride, chloride, bromide or iodide.

Preferably, Het is one of the followingrings: pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, oxazolinyl, thiazolinyl, pyrazinyl, tetrazolyl, triazolyl, pyrrolidinyl, piperazinyl, thienyl, furyl, azetidinyl and imidazolinyl. Each of these rings may be substituted by one or more of the following: alkyl, phenyl or phenylalkyl. The preferred substituents are methyl, phenyl or benzyl.

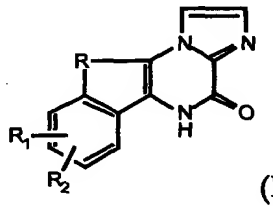
The preferred polyfluoroalkoxy groups are the trifluoromethoxy groups.

The compounds of the formula (I) in which R_7 is NO-alk, $C(COOR_{10})R_{20}$, $C(CONR_{10}R_{21})R_{20}$ or CHR_{19} can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

The compounds of the formula (I), in which R is $CH\text{-}R_6$ and R_6 is $-CO\text{-}COOR_{10}$, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures.

The compounds of the present invention include the eniantomers and diastereoisomers of the compounds of the formula (I), in which R is $C(R_4)R_5$ or $CH\text{-}R_6$.

(31) Imidazo(1,2-a)indeno(1,2-e)pyrazin-4-one derivatives and their salts in WO 95-26350 as shown below:



(I)

Imidazo(1,2-a)indeno(1,2-e)pyrazin-4-one derivatives having general formula (I) wherein R is $C=R_3$, $C(R_4)R_5$ or $CH-R_6$, R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, amino, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl, SO_3H, hydroxy, polyfluoralkoxy, $-COOR_7$, $-NH-CO-NR_8R_9$, $-N(alk)-CO-NR_8R_9$, $-N(alk-Ar)-CO-NR_8R_9$, $-NH-CS-NR_8R_9$, $-N(alk)-CS-NR_8R_9$, $-NH-CO-NR_{18}$, $-NH-CS-R_{19}$, $-NH-C(=NR_{20})-NR_7R_9$, $-N(alk)-C(=NR_{20})-NR_7R_9$, $-NH-SO_2-NR_7R_9$, $N(alk)-SO_2-NR_7R_9$, $-CO-NR_7R_9$, $-NH-SO_2-CF_3$, $-NH-SO_2-alk$, $-NR_9R_{11}$, $S(O)_m$-alk-Ar, $-SO_2-NR_7R_9$, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R_3 is NO-alk, CHR_{10}, NR_7, $C(COOR_7)R_{16}$ or $C(CONR_7R_{15})R_{16}$, R_4 is alkyl, -alk-Het, -alk-Het" or phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_7$ and $-alk-COOR_7$, R_5 is $-NR_{12}R_{13}$, -NH-CHO, -NH-CHO, $-NH-COOR_{17}$, $-NH-SO_2R_{19}$, $-COOR_7$, $-alk-COOR_7$, $-alk-CONR_7R_{15}$, $-alk-NR_7R_{15}$, -alk-OH, -alk-CN, -alk-Het", phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_7$ and $-alk-COOR_7$, -NH-CO-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_7$ and $-alk-COOR_7$, -NH-CO-Het, -NH-CO-Het", -NH-CO-alk-Het, -NH-CO-alk-Het", $-NH-CO-alk-COOR_7$, $-NH-CO-alk-NR_7R_{15}$, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_7$, and $-alk-COOR_7$, $-NH-CO-C(Ar)(CF_3)OCH_3$, pyrrolyl-1which may be substituted by $-COOR_7$, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_7$, and $-alk-COOR_7$, -NH-CO-NH-Het, -NH-CO-NH-Het", -NH-CO-NH-alk-Het, -NH-CO-NH-alk-Het", -NH-CO-NH-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_7$, and -alk-

$COOR_7$, -NH-COalk, -NH-COcycloalkyl, -NH-CO-NH-alk or -NH-CO-NH_2, R_6 is -NH-CHO, -COOalk, -alk-$COOR_7$, -alk-CO-NR_7R_{15}, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_7$, and -alk-$COOR_7$, -R_{14}-$COOR_7$, -CO-$COOR_7$, -NH-$COOR_{17}$, -NH-CO-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_7$, and -alk-$COOR_7$, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-Het", -NH-CO-alk-Het", -NH-CO-alk(C_2-C_6)-$COOR_7$, -NH-CO-alk(C_2-C_6)-NH_2, -NH-CO-alk-N(alk)$_2$, -NH-CO-alk-NHalk, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_7$, and -alk-$COOR_7$, -NH-CO-C(Ar)(CF_3)OCH_3, -alk-Het", pyrrolyl-1- may be substituted by -$COOR_7$, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_7$, and -alk-$COOR_7$, -NH-CO-NH-alk-Het, -NH-CO-NH-alk-Het", -NH-CO-NH-Het", or -NH-CO-NH-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_7$, and -alk-$COOR_7$, R_7 is hydrogen or alkyl, R_8 is hydrogen, alkyl, -alk-$COOR_7$, -alk-Het", -alk-Het, -alk-NR_9R_7 or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_7$, cyano, -alk-$COOR_7$, or phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_7$, cyano, -alk-$COOR_7$, -Het or -Het", R_9 is hydrogen or alkyl, R_{10} is -alk-$COOR_7$, -Het", -alk-Het", phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, $COOR_7$, cyano, -alk -$COOR_7$, or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_7$, cyano, -alk--$COOR_7$, R_{11} is alkyl, -Het, -Het" or alkylcarbonyl, R_{12} is hydrogen, alkyl, -alk-$COOR_7$, -alk-NR_7R_{15}, -alk-Het, -alk-Het", or phenylalkyl in which the phenyl group

may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano, and -alk-$COOR_7$, R_{13} is hydrogen or alkyl, R_{14} is a -CHOH- or -CHOH-alk(C_1-C_5) chain, R_{15} is hydrogen or alkyl, R_{16} is hydrogen or alkyl, R_{17} is alkyl or phenylalkyl, R_{18} is hydrogen, or an alkyl moiety (the term C_1-C_9 alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), alkoxy, -alk-$COOR_7$, -alk-Het", -alk-Het, , -alk-NR_9R_7, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_7$, cyano and -alk-$COOR_7$, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, cyano, -alk-$COOR_7$, Het or Het", R_{19} is alkyl or phenyl, R_{20} is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene moiety. The term alk' refers to an alkyl moiety. The term Ar refers to a phenyl moiety. m = 0,1 or 2. The term Het refers to a heterocycle which is mono- or poly-saturated or unsaturated with four to nine carbon atoms and one or more heteroatom (O, S, N). The term Het" refers to a heterocycle which is mono- or poly-saturated or unsaturated with one to three carbon atoms and one or more heteroatom (O, S, N)may be substituted with one or - or poly-saturated or insaturated with four to nine carbon atoms and one or more heteroatom (O, S, N)may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl. Provided that when R_1 and R_2 are hydrogen, R is CHR_6, R_6 is alk-Het" in which alk is alkyl (C_1) and Het" is not 2-imidazol.

Unless otherwise stated, in the above and below definitions, the alkyl or alkylene moieties are a straight or branched chain having one to six carbon atom, the cycloalkyl moieties have three to six carbon atoms and the halogen atoms are selected from the following: fluoride, chloride, bromide, or iodide.

Preferably, Het is one of the following cycles: pyrrolyl, pyridyl, pyrimidinyl, morpholinyl, pyrazinyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl and furyl. Het" is one of the following: pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl,

thiazolinyl, pyrazinyl, tetrazolyl, triazolyl, oxazolyl, pyrrolidinyl, azetidinyl, piperazinyl, piperidinyl, thienyl, oxazolinyl, furyl and imidazolinyl. Each of these rings may be substituted by one or more of the following: alkyl, phenyl or phenylalkyl. The preferred substitutants are methyl, phenyl or benzyl.

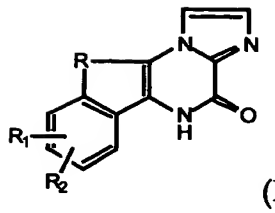
The prefered polyfluoroalkoxy groups are the trifluoromethoxy groups. The compounds of the formula (I) in which R_3 is NO-alk, $C(COOR_7)R_{16}$, $C(CONR_7R_{15})R_{16}$ or CHR_{10} can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

The compounds of the formula (I), in which R is $CH\text{-}R_6$ and R_6 is $-CO\text{-}COOR_7$, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures.

The compounds of the present invention include the eniantomers and diastereoisomers of the compounds of the formula (I), in which R is $C(R_4)R_5$ or $CH\text{-}R_6$.

The compounds of of the present invention include compounds of the formula (I) in which R, R_1 and R_2 are as defined previously except for when: a) R_1 and R_2 are hydrogen, R is CHR_6, R_6 is -alk-Het" in which alk is an alkyl moiety (C_1) and Het" is a 2-imidazolyl moiety, b) R_1 and R_2 are hydrogen, R is CHR_6, R_6 is -NHCHO or alk-$COOR_7$ in which R_7 is hydrogen or a terbutyl group, c) R_1 and R_2 are hydrogen, R is $C{=}R_3$, R_3 is CHR_{10} and R_{10} is a 2-imidazolyl moiety, d) R_1 is hydrogen, R_2 is CHR_6 and R_6 is -NHCHO. The preferred compounds are those with R_1 in position -7 or -8.

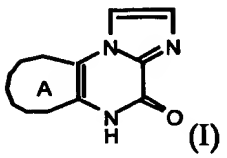
(32) Indeno[1,2-e]pyrazine-4-one (I) in WO 95-26349 as shown below:



(I)

Indeno[1,2-e]pyrazine-4-one of formula (I), wherein R is a substituted nitrogen, oxygen or sulphur atom or a radical C=R_3, C(R_4)R_5 or CH-R_6; R_1 is a hydroxy radical, polyfluoroalkoxy, carboxy, alkoxycarbonyl, -NH-CHO or -NH-CO-N(alk)Ar where Ar is optionally substituted, -N(alk)-CO-NR_8R_9, -N(alk-Ar)-CO-NR_8R_9, -NH-CO-NR_9R_{12}, -NH-CS-NR_8R_9, -N(alk)-CS-NR_8-R_9, -NH-CO-R_{10},-NH-CS-R_{20},-NH-C(=NR_{21})-NR_7R_9,-N(alk)-C(=NR_{21})-NR_7R_9,-NH-SO_2-NR_7R_9, N(alk)-SO_2-NR^7R^9, -CO-NR_7R_9, -NH-SO_2-CF_0, -NH-SO_2-alk, -NR_9R_{11}, -S(O)$_m$-alk-Ar, -SO_2-NR_7R_9, optionally 3-substituted 2-oxo-1 imidazolidinyl or optionally 3-substituted 2-oxo-1 perhydropyrimidinyl; R_2 is a hydrogen or halogen atom or an akyl radical, alkoxy, amino, -NH-CO-NH-Ar, N=CH.N(alk)alk', nitro, cyano, phenyl, imidazolyl, acylamino, SO_3H, hydroxy, polyfluoroalkoxy, carboxy, alkoxycarbonyl, -NH-CHO, -NH-CO-N(alk)Ar where Ar is optionally substituted, -N(alk)-CO-NR_8R_9, -N(alk-Ar)-CO-NR_8R_9, -NH-CO-NR_9R_{12} -NH-CS-NR_8R_9, -N(alk)-CS-NR_8R_9, -NH-CO-R_{10}, -NH-CS-R_{20}, -NH-C(=NR_{21})-NR_7R_9,-N(alk)-C(=NR_{21})-NR_7R_9, -NH-SO_2-NR_7R_9, -N(alk)-SO_2-NR_7R_9, -CO-NR_7R_9, -NH-SO_2-CF_3, -NH-SO_2-alk, -NR_9R_{11}, -S(O)$_m$-alk-Ar, -SO_2-NR_7R_9, optionally 3-substituted 2-oxo-1-imidazolidinyl or optionally 3-substituted 2-oxo-1-perhydropyrimidinyl; R_3 is an oxygen atom or a NOH, NO-alk-COOX or CH-R_{13} radical, R^4 is an alkyl radical; -alk-Het or -alk-Ar; R_5 is a straight or branched C_{1-11} alkyl radical, -alk-Het or -alk-Ar, or R_4 and R_5, taken together with the carbon atom to which they are attached, form a cycloalkyl radical; R_6 is a hydrogen atom radical or a hydroxy radical, straight or branched C_{1-11} alkyl, -$NR_{14}R_{15}$, -alk-OH, -alk-$NR_{14}R_{15}$, -alk-Ar or -alk-Het; and salts thereof.

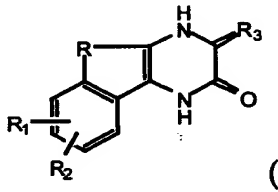
(33) Imidazo[1,2-a]pyrazine-4-one derivatives (I) in WO95-26352 as shown below:



(I)

Compounds of formula (I), wherein ring A is selected from rings 1, 2 and 3, wherein R is a CH_2 radical or a sulphur, oxygen or nitrogen atom substituted by an alkyl radical, and salts thereof.

(34) 5H-Indeno[1,2-b]pyrazine-2,3-dione derivatives and their salts (I) in WO 95-26342 as shown below:



(I)

5H-Indeno[1,2-b]pyrazine-2,3-dione of formula (I), wherein R isN-alk, $C(R_4)R_5$, CH-R_6 or $C=R_7$, R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, amino, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl, SO_3H, hydroxy, polyfluoralkoxy, carboxy, alkylcarbonyl, -NH-CO-$NR_{11}R_{12}$, -N(alk)-CO-$NR_{11}R_{12}$, -N(alk-Ar)-CO-$NR_{11}R_{12}$, -NH-CS-$NR_{11}R_{12}$, -N(alk)-CS-$NR_{11}R_{12}$, -NH-CO-NR_{11}, -NH-CS-R_{24}, -NH-C(=NR_{27})-$NR_{10}R_{12}$, -N(alk) C(=NR_{27})-$NR_{10}R_{12}$,, -CO-$NR_{10}R_{12}$, -NH-SO_2-$NR_{10}R_{12}$, N(alk)-SO_2-$NR_{10}R_{12}$, -NH-SO_2-CF_3, -NH-SO_2-alk, -$NR_{10}R_{13}$, $S(O)_m$-alk-Ar, -SO_2-$NR_{10}R_{12}$, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R_3 is oxygen, NOH, NOalk or NOalkAr, R_4 is alkyl, -alk-Het or phenylalkyl

in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, R_5 is an alkyl group (the term C_1-C_{11} alkyl represents a straight or branched alkyl chain having one to eleven carbon atoms), -alk-Het, NR_8R_9, -NH-CHO, -NH-$COOR_{17}$, -NH-SO_2R_{24}, -$COOR_{10}$, -alk-$COOR_{10}$, -alk-$CONR_{10}R_{18}$, -alk-$NR_{10}R_{18}$, -alk-OH, -alk-CN, phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-$COOR_{10}$, -NH-CO-alk-$NR_{10}R_{18}$, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, pyrrolyl-1wich may be substituted by -$COOR_{10}$, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-CO-NH-Het, -NH-CO-NH-alk-Het, -NH-CO-NH-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -NH-COalk, -NH-COcycloalkyl, -NH-CO-NH-alk or -NH-CO-NH_2, or R_4 and R_5, together with the carbon atom they attached to, are a cycloalkyl group, R_6 is hydrogen, hydroxy, alkyl (the term C_1-C_{11} alkyl represents a straight or branched alkyl chain having one to eleven carbon atoms), -alk-OH, -$NR_{14}R_{15}$, -alk-$NR_{14}R_{15}$,, alk-Het, -NH-CHO, -COOalk, -alk-$COOR_{10}$, -alk-CO-$NR_{10}R_{18}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$, and -alk-$COOR_{10}$, -R_{16}-$COOR_{10}$, -CO-$COOR_{10}$ or pyrrolyl-1may be substituted by -$COOR_{10}$, R_7 is oxygen or NOH, NO-alk-$COOR_{10}$, NO-alk, CHR_{19}, $C(COOR_{10})R_{20}$ or $C(CONR_{10}R_{21})R_{20}$, R_8 is hydrogen, alkyl, -alk-$COOR_{10}$, -alk-$NR_{10}R_{21}$, -alk-Het or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy,

nitro, amino, hydroxy, cyano, -alk-NH_2, -$COOR_{10}$ and -alk-$COOR_{10}$, R_9 is hydrogen or alkyl, R_{10} is hydrogen or alkyl, R_{11} is hydrogen, alkyl (the term C_1-C_9 alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), alkoxy, -alk-$COOR_{10}$, alk-Het, -alk-$NR_{12}R_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano and -alk-$COOR_{10}$, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, carboxy, alkoxycarbonyl, cyano and -alk-$COOR_{10}$ or -Het, R_{12} is hydrogen or alkyl, R_{13} is alkyl, Het or alkoxycarbonyl, R_{14} and R_{15} are the same or different and are each an alkyl group or R_{14} is hydrogen and R_{15} is hydrogen, alkyl, -COR_{22}, -CSR_{23} or SO_2R_{24}, R_{16} is a -CHOH or -CH(OH)alk(C_1-C_5) chain, R_{17} is alkyl or phenylalkyl, R_{18} is hydrogen or alkyl, R_{19} is hydroxy, alkyl, alk-Het, -$NR_{25}R_{26}$, -alk-$COOR_{10}$, -Het , phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$ or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, R_{20} is hydrogen or alkyl, R_{21} is hydrogen or alkyl, R_{22} is alkyl, cycloalkyl, -COOalk, -alk-$COOR_{10}$, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, -alk-$NR_{10}R_{12}$, -NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, -phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano, and -alk-$COOR_{10}$, -Het, -alk-Het, -OR_{17}, -NH-alk-Ar in which Ar may be substituted by one or more of the following: halogen,

alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH_2, -$COOR_{10}$, cyano and -alk-$COOR_{10}$, NH-alk-Het, -NH-alk, -NH_2 or -NH-Het, R_{23} is -NH-alk, -NH-Ar, -NH-Het or -NH_2, R_{24} is alkyl or phenyl, R_{25} and R_{26} are the same or different and are each alkyl or cycloalkyl, R_{27} is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene group. The term alk' refers to an alkyl group. m = 0,1 or 2. The term Ar refers to a phenyl group. The term Het refers to a heterocycle which is mono or poly saturated or unsaturated with four to nine carbon atoms and one or more heteroatom (O, S, N) may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl. Provided that when R_1 and R_2 are hydrogen and R_3 is oxygen, R is not (a) C=R_7 in which R_7 is oxygen or NOH, (b) CH-R_6 in which R_6 is hydroxy.

Unless otherwise stated, in the above and below definitions, the alkyl or alkylene groups are a straight or branched alkyl chain having one to six carbon atom, the acyl groups have two to four carbon atoms, the cycloalkyl groups have three to six carbon atoms and the halogen are of the following: fluoride, chloride, bromide, or iodide.

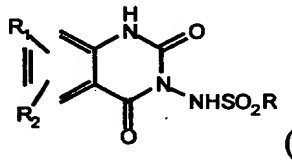
Preferably, Het is one of the following rings: pyrrolyl, pyridyl, pyrimidinyl, thiazolyl, oxazolinyl, thiazolinyl, pyrazinyl, tetrazolyl, triazolyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl, furyl, azetidinyl, imidazolinyl. Each of these rings may be substituted by one or more of the following: alkyl, phenyl or phenylalkyl. The preferred substituents are methyl, phenyl or benzyl.

The preferred polyfluoroalkoxy groups are the trifluoromethoxy groups. The compounds of the formula (I) in which R is C=R_7 , with R_7 being NO-alk, C($COOR_{10}$)R_{20}, C($CONR_{10}R_{21}$)R_{20} or CHR_{19} and/or with R_3 being NOH, NOalk or NOalkAr, can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

The compounds of the formula (I), in which R is CH-R_6 and R_6 is -CO-$COOR_{10}$, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures. The compounds of the present

invention include the enantiomers and diastereoisomers of the compounds of the formula (I), in which R is $C(R_4)R_5$ or $CH\text{-}R_6$.

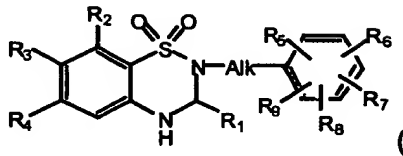
(35) Quinazoline-2,4-dione (I) in WO 95-19346 as shown below:



(I)

Compounds of formula I wherein R is (C_{1-6}) alkyl or phenyl optionally mono-, di- or trisubstituted by halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, nitro, trifluoromethyl, amino, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, cyano, (C_{1-4})alkylsulfonyl, phenylsulfonyl or sulfonylamino, R_1 and R_2 independently are hydrogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{2-5})alkenyl, halogen, trifluoromethyl, nitro, amino, (C_{1-4})alkylamino, benzyloxy, benzoylamino, carboxy, cyano, (C_{1-4})alkoxy-carbonyl, (C_{1-4})alkylsulfonyl, phenylsulfonyl, sulfonylamino, (C_{2-5})alkanoylamino or phenyl optionally substituted by (C_{1-4})alkyl, halogen or nitro, provided that R_1 and R_2 are not both hydrogen if R is unsubstituted phenyl, or R_1 and R_2 on adjacent carbon atoms together form a group -CH=CH-CH=CH-, or a salt thereof. Alkyl and alkoxy groups and moieties in the compounds of formula I may be straight - or branched-chained. Halogen means fluorine, chlorine, bromine or iodine. The compounds of formula I may form cationic salts, e.g. alkali metal or ammonium salts deriving from the sulfonamido group or when a carboxyl group is present. Depending on the nature of the substituents defined above, the compounds of formula I may also form acid addition salts. The tautomeric forms of the compounds of formula I are also embraced.

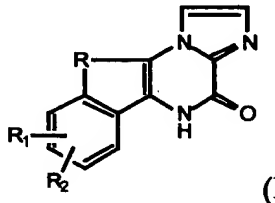
(36) 3,4-Dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide-3-carboxylic acid derivatives (I) in WO 95-07899 as shown in below:



(I)

Compounds of formula (I) wherein R_1 is a carboxy, alkoxycarbonyl, tetrazolyl, -CO-NH_2, -CO-NH-alk, -CO-N(alk)$_2$ -CO-NHOH, -CO-N(alk)OH, -CO-NH-O-R_{10}, -CO-N(alk)-OR_{10} radical or a group convertible in vivo into a carboxy radical, R_2, R_3 and R_4, which are the same or different, are hydrogen or halogen atoms or alkyl or alkoxy radicals, R_5 is a hydroxy, -NHOH, -NH-CO-NH_2, -CH_2-NH_2, hydroxyalkyl, alkoxyalkyl, or -alk=NOH radical, R6, R7, R8 and R9, which are the same or different, are hydrogen or halogen atoms or alkyl, alkoxy, polyfluoroalkyl, amino, nitro, cyano, vinyl, polyfluoroalkoxy, alkoxycarbonyl, carboxy, phenylalkyloxy, phenylalkyl, benzoylamino,phenylcarbonyl, hydroxy, -NHOH, -NH-CO-NH2, -CH2-NH2, hydroxyalkyl, alkoxyalkyl, -alk=NOH or phenoxy, with the phenyl ring being optionally substituted by one or several substituents selected from the halogen atoms and the alkyl, alkoxy or polyfluoroalkyl radicals, R_{10} is an alkyl or phenylalkyl radical and alk is an alkyl or alkylene radical. The invention also concerns the salts of thereof, the preparation thereof, and drugs containing same.

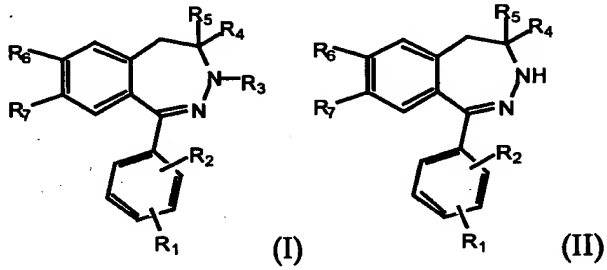
(37) Imidazo(1,2-a)pyrazin-4-one derivatives (I) in WO95-02602 as shown below.



(I)

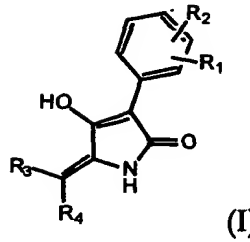
Compounds of formula (I), wherein R is an oxygen or sulphur atom or an NH or N-alk radical, and each of R_1 and R_2, which are the same or different , is a hydrogen or halogen atom or an alkyl, alkoxy, amino, acylamino, -NH-CO-NH-Ar,-N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl or SO_3H radical, the preparation thereof, and drugs containing such compounds.

(38) 2,3-Benzodiazepine derivatives (I) and (II) in GB 2 311 779 A as shown below.



Non-competitive AMPA antagonistic compounds of the formula I, wherein R^1 and R^2 represent, independently, a hydrogen, a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a trifluoromethyl group or a group of the formula $-NR^8R^9$, wherein R^8 and R^9 stand, independently, for a hydrogen, a C_{1-4} alkyl group or a group of the formula $-COR^{10}$, wherein R^{10} is a hydrogen, a C_{1-6} alkyl group that can be substituted, a C_{6-10} aryl group, a C_{1-4} alkoxy group, a C_{3-5} cycloalkyl group, a C_{2-6} alkenyl group a C_{3-5} cycloalkoxy group or a group of the formula $-NR^{11}R^{12}$, wherein R^{11} and R^{12} mean, independently, a hydrogen, a C_{1-4} alkyl group, a C_{3-5} cycloalkyl group or a C_{6-10} aryl group, R^3 represents a C_{1-4} alkyl groups a C_{3-5} cycloalkyl group or a group of the formula $-CO-R^{13}$, wherein R^{13} has the same definitions given in relation to R^{10}, R^4 and R^5 mean, independently, a hydrogen or a C_{1-3} alkyl group, R^6 and R^7 are, independently, a hydrogen, a chloro or a bromo, with the provision that if one of R^6 and R^7 stands for a hydrogen, the other is different from hydrogen, as well as the isomers thereof and the acid addition salts of the compounds or the isomers.

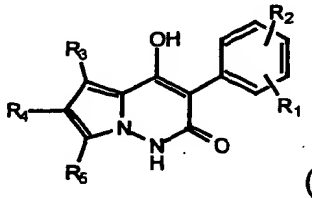
(39) Tetramic acid derivatives (I) in GB 2 266 888 A as shown below:



(I)

Wherein R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; R^3 and R^4 independently represent hydrogen, hydrocarbon, a heterocyclic group, trifluoromethyl, $-OR^c$, $-SR^c$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$, provided that R^3 does not represent C_{2-5} alkoxycarbonyl when R^4 represents an optionally substituted phenyl group; R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group; and R^c represents hydrocarbon or a heterocyclic group.

(40) Pyrrolo-pyridazinone derivatives (I) in GB 2 265 372 A as shown below:

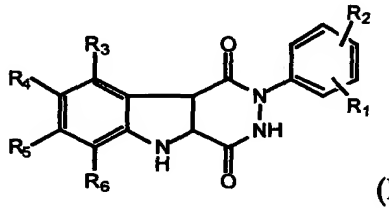


(I)

Pyrrolo-pyridazinone derivatives, wherein R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, -

COR^a, $-CO_2R^a$ or $-CONR^aR^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $CONR^aR^b$; and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

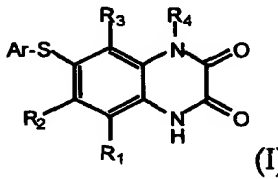
(41) 2-Phenylpyridazino[4,5-b]indole-1,4-dione derivatives (I) in GB 2 290 292 A as shown below:



(I)

Compound of formula I, or a salt or prodrug thereof: wherein R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; R^3, R^4, R^5 and R^6 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$,$-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

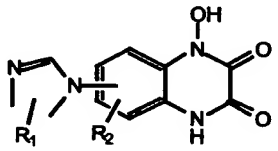
(42) Arylthioxaline derivatives (I) in Tokkaihei 8-59660 as shown below:



(I)

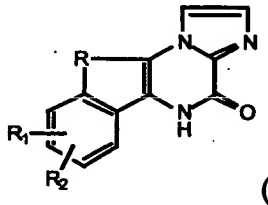
Arylthioxaline derivatives of the formula (I) and its related salts, wherein R1 is hydrogen, halogen, or nitro, R2 is hydrogen, halogen, nitro, cyano, or trihalogenomethyl, R3 is hydrogen, halogen, or nitro, R4 is hydrogen, optionally substituted lower alkyl, or optionally substituted lower cycloalkyl, and Ar is optionally substituted aromatic heterocyclic ring having at least one nitrogen atom.

(43) Hydroxyquinoxalinedione derivatives in Tokkaihei 7-165756 as shown below:



The present invention relates to hydroxyquinoxalinedione derivatives of the above formula and its related salt, wherein R1 is hydrogen or lower alkyl, and R2 is nitro or trifluoromethyl.

(44) Imidazo[1,2-a]pyrazin-4-one (I) in WO 95-02601 as shown below:

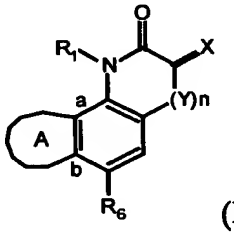


(I)

Compounds of formula (I), wherein either R is C=R_3, C(R_4) R_5 or CH- R_6, R_1 and R_2 are hydrogen, halogen, alkyl, alkoxy, amino, acylamino, -NH-CO-NH-Ar, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl or SO_3H, R_3 is oxygen, NOH, NO-alk-COOK or CH-R_7, R_4 is alkyl, -alk-Het or alk-Ar, R_5 is alkyl, -alk-Ar, or C(R_4) R_5 is cycloalkyl, R_6 is hydroxy, alkyl, NR_8 R_9 , -alk-OH,-alk-NR_8 R_9 , -alk-Ar or -alk-Het, R_7 is hydroxy, alkyl, phenyl, -alk-Ar, -alk-Het, NR_{10} R_{11} or a heterocyclic ring, R_8 and R_9 are alkyl, or R_8 is hydrogen and R_9 is hydrogen or alkyl, -COR_{12}, -CSR_{30} or -SO_2 R_{13}, R_{10} and R_{11} are alkyl or cycloalkyl, R_{12} is alkyl, cycloalkyl, phenyl, -COO-

alk, -CH_2-COOX, -CH_2-NH_2 , -NH-alk, -NH-Ar, -NH_2 or -NH-Het, R_{13} is alkyl or phenyl, R_{30} is -NH-alk, -NH-Ar, -NH_2 or -NH-Het; or R is a 2-imidazolylmethyl radical and each of R_1 and R_2 is a hydrogen atom.

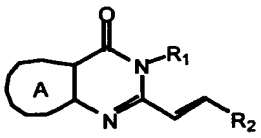
(45) AMPA antagonists (I) in WO 94-26747 as shown below:



(I)

Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R^1 is hydrogen, alkyl, or benzyl; X is O or NOR^2 , wherein R^2 is hydrogen, alkyl or benzyl; Y is N-R^4 wherein R^4 is hydrogen, OH or alkyl; n is 0 or 1; R^6 is phenyl, naphthyl, thienyl, pyridyl, all of which may be substituted one or more times with substituents selected from the group consisting of halogen; CF_3, NO_2, amino, alkyl, alkoxy and phenyl; A is a ring of five to seven atoms fused with the benzo ring at the positions marked a and b.

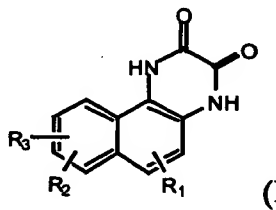
(46) 2,3-Disubstituted-(5,6)-heteroarylfused-pyrimidine-4-ones in EP 0807 633 A2 as shown below:



2,3-Disubstituted-(5,6)-heteroaryl fused-pyrimidine-4-ones of formula (I) and their salts are new: ring A = a group of formula (i) or (ii) both optionally substituted by H, 1-6C alkyl, halo, CF_3, $(CH_2)_nNH_2$, (1-6C alkyl)amino$(CH_2)_p$, di(1-6C alkyl)amino$(CH_2)_n$, 1-6C alkoxy, 1-6C hydroxyalkyl, (1-6C alkyl)O(1-6C alkyl), CN,

(1-6C alkyl)COO(1-6C alkyl), (1-6C alkyl)OCOO(1-6C alkyl), (1-6C alkyl)COO, OH, NO_2, R^3CO, R^4OCO, di(1-6C alkyl)NCO, 1-6C cycloalkyl, R^4NHCO or phenyl (optionally substituted); A, B, D, E = C or N; F, G, J = C, N, O or S with proviso; R^1 = Ph1 or pyridin-2-yl, pyridin-3-yl or pyridin-4-yl optionally substituted; Ph1 = a group of formula (iii); R^2 = Ph2 or a group of formula (iv) or (v); K, L, M = C or N provided that only one is N; P, Q, T = C, N, O or S provided that only one can be O or S and that at least one is a heteroatom; Ph2 = a group of formula (vi); R^3, R^4 = H or 1-6C alkyl; R^5 = H, 1-6C alkyl, halo, CF_3, 1-6C alkoxy or 1-6C alkylthio; R^6-R^8 = H or halo; R^9 = e.g.H, 1-6C alkyl (optionally substituted), halo, CF_3, 1-6C alkoxy (optionally substituted), 1-6C alkylthio, $(CH_2)_pOR^{13}$, $(CH_2)_pNH$(1-6C alkyl), $(CH_2)_nN$(1-6C alkyl)$_2$, $(CH_2)_pNH$(1-5C cycloalkyl) (sic), $(CH_2)_pCONH_2$, $(CH_2)_n$-CONH(1-6C alkyl), $(CH_2)_pCON$(1-6C alkyl)$_2$, $(CH_2)_pCONH$(1-5C cycloalkyl) (sic), $(CH_2)_pCOOR^{13}$, (1-6C alkyl)OCO(1-6C alkyl), (1-6C alkyl)OCOO(1-6C alkyl), OCO(1-6C alkyl), $(CH_2)_pNHCO$(1-6C alkyl) or CN; R^{10}, R^{14} = e.g. H, 1-6C alkyl (optionally substituted), halo, CF_3, 1-6C alkoxy (optionally substituted), 1-6C alkylthio, $(CH_2)_pOR^{13}$, $(CH_2)_nNH$(1-6C alkyl), $(CH_2)_pN$(1-6C alkyl)$_2$, $(CH_2)_pNH$(1-5C cycloalkyl) (sic), $COO(CH_2)_pR^4$, $(CH_2)_pNH_2$, 1-6C hydroxyalkyl, (1-6C alkyl)O(1-6C alkyl), CHO or CN; R^{11}, R^{12} = H or halo; R^{13} = H, 1-6C alkyl, CO(1-6C alkyl), COO(1-6C alkyl), CONH(1-6C alkyl) or CON(1-6C alkyl)$_2$; R^{15}-R^{17} = H, CN, 1-6C alkyl, halo, CF_3, CHO or 1-6C alkoxy; n, p = 0-3; provided that when R^9 = H then one of R^{11} and R^{12} is not H.

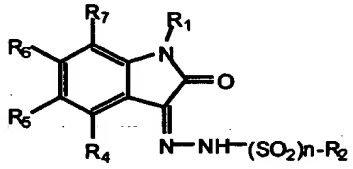
(47) Quinoxaline compounds (I) in EP 0 511 152 A2 as shown below:



(I)

Quinoxaline compounds having the formula I wherein R^1 is H, NO_2, CN, CF_3 or halogen, R^2 and R^3 independently are H, CN, CF_3, halogen, C(NOH) C_{1-6} -alkyl, COR^4 or SO_2R^4 wherein R^4 is C_{1-6} -alkyl-, optionally substituted, or NR^5R^6 wherein R^5, R^6 independently are H, C_{3-6} -cycloalkyl, is C_{1-6}-, optionally substituted, compositions thereof and methods of preparing the compounds are described.

(48) Hydrazone derivatives in EP 0 503 349 A1 as shown below:

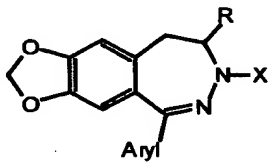


(I)

Hydrazone derivatives having the formula (I) wherein n is 0 or 1; R^1 is hydrogen, C_{1-6} -alkyl which may be branched, C_{3-7} -cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6} -alkoxy, CH_2CO_2 R' is hydrogen or C_{1-6} -alkyl which may be branched, CH_2CN, CH_2CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C_{1-6} -alkyl, or $CH_2C(=NOH)$- NH_2; R^2 is pyridyl or phenyl, both of which may be substituted one or more times preferably into the ortho and para positions with halogen, CF_3, NO_2, CN, phenyl, $SO_2NR''R'''$ wherein R'' and R''' independently are hydrogen, benzyl, or C_{1-6} -alkyl; R^4, R^5, R^6, R^7 independently are hydrogen, C_{1-6} -alkyl which may be branched, phenyl, halogen, C_{1-6} -alkoxy, NO_2, CN, CF_3, or $SO_2NR^{11}R^{12}$ wherein R^{11} and R^{12} independently are hydrogen, benzyl, or C_{1-6} -alkyl; or R^6 and R^7 together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, SO_2NR^{13} R^{14} wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6} -alkyl;, and R^4 and R^5 have the meanings set forth above; or R^4 and R^5 together form an additional 4 to 8 membered carbocyclic ring whihc may be aromatic or partial saturated and which may be substituted with halogen,

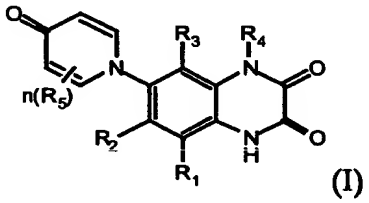
NO_2, CF_3, CN, SO_2NR^{13} R^{14} wherein R^{13} and R^{14} independently are hydrogen, benzyl, or C_{1-6} -alkyl;, and R^6 and R^7 have the meanings set forth above.

(49) Dihydro-2,3-benzodiazepine derivatives (I) in EP 0 699 676 A1 as shown below:



Dihydro-2,3-benzodiazepine derivatives represented by the formula I wherein R is methyl, X is acetyl and Aryl is p-nitrophenyl.

(50) Oxopyridinylquinoxaline derivatives (I) in EP 0 676 397 A1 as shown below:

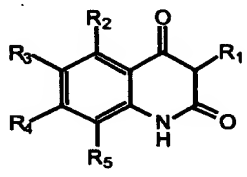


(I)

An oxopyridinylquinoxaline derivative represented by the following formula I or pharmaceutically acceptable salts thereof wherein R^1 is hydrogen, halogen, nitro or trihalomethyl; R^2 is hydrogen, halogen, nitro, cyano, trihalomethyl, carbamoyl, carbomoyl substituted with lower alkyl, sulfamoyl, or sulfamoyl substituted with lower alkyl; R^3 is hydrogen, nitro, or halogen; R^4 is hydrogen, lower alkyl, substituted lower alkyl, lower cycloalkyl, or substituted lower cycloalkyl; R^5's are substituents independently selected from the group consisting of halogen, nitro,

cyano, lower alkyl, carbamoyl, and carbamoyl substituted with lower alkyl; and n is an integer of 0 to 4.

(51) Dioxo-tetrahydroquinoline derivatives (IA) in EP 0 459 561 A2 as shown below:

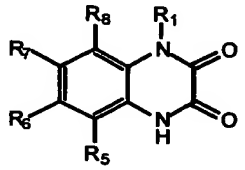


(IA)

Dioxo-tetrahydroquinoline derivatives of formula (IA), wherein R^1 is a group of part formula (I) and (II); wherein U and V independently represent cyano, carboxy, -COR^6, -CO_2 R^6, -CO_2 SR^6, -CONHOH or -$CONHNH_2$; n is zero or 1, preferably zero; T represents cyano, carboxy, -COR^6, -CO_2 R^6, -CONHOH or -$CONHNH_2$ or a group of formula in which the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; B represents a bond or a carbonyl group (C=O); W, X, Y and Z represent oxygen, sulphur, nitrogen or carbon, provided that no more than one of W, X, Y and Z represents oxygen or sulphur, at least one of W, X, Y and Z represents carbon and at least one of W, X, Y and Z is other than carbon; one of E, F and G represents nitrogen or carbon and the remainder represent carbon; A^1, A^2 and A^3 represent one, two or three substituents not exceeding the maximum number permissible by the disposition of heteroatoms in the five- or six-membered ring, which substituents are independently selected from hydrogen, hydrocarbon, halogen, cyano, trifluoromethyl, nitro, -OR^a, - SR^a, -SOR^a, -SO_2 R^a, SO_2 NR^aR^b, - NR^aR^b, -NR^a COR^b, -$NR^aCO_2R^b$, COR^a, -CO_2 R^a or -$CONR^aR^b$; or A^1 and A^2 or A^2 and A^3 together represent the residue of an aromatic or heteroaromatic ring; R^2, R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, halogen, cyano, trifluoromethyl, nitro, -OR^a, - SR^a, -SOR^a, -SO_2R^a, $SO_2NR^aR^b$, - NR^aR^b, -NR^a COR^b, -$NR^aCO_2R^b$, COR^a, -CO_2 R^a or -$CONR^aR^b$; or R^2 and R^3, R^3 and R^4 or R^4 and R^5 together represent the residue of an aromatic or

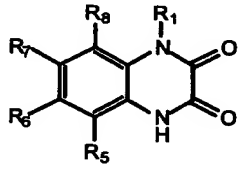
heteroaromatic ring; R^6 represents hydrocarbon; and R^a and R^b independently represent hydrogen or hydrocarbon.

(52) Quinoxaline derivatives in EP 0 377 112 A1 as shown below:



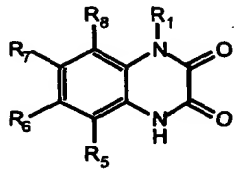
Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is hydroxy, alkoxy, aryloxy, aralkyloxy, cycloalkylalkoxy, cycloalkoxy, or acyloxy; and R^5, R^6, R^7 and R^8 independently are hydrogen, NO_2, halogen, CN, SO_2 NR'R', SO_2 R', CF_3, or OR', wherein R' is hydrogen or C_{1-4}-alkyl.

(53) Quinoxaline derivativess in EP 0 374 534 A1 as shown below:



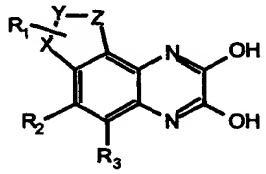
Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is hydroxy, alkoxy, aryloxy, aralkyloxy, cycloalkylalkoxy, cycloalkoxy, or acyloxy; R^5 and R^6 together form a further fused ring, which may be substituted with hydrogen, halogen, or CN, and R^7 and R^8 independently are hydrogen, NO_2, halogen, CN, SO_2 NR'R', SO_2 R', CF_3, or OR', wherein R' is hydrogen or C_{1-4}-alkyl; or R^7 and R^8 together form a further fused ring, which is substituted with hydrogen, halogen, or CN, and R^5 and R^6 independently are hydrogen, NO_2, halogen, CN, SO_2 NR'R', SO_2 R', CF_3, or OR', wherein R' is hydrogen or C_{1-4}-alkyl.

(54) Quinoxaline derivatives in EP 0 315 959 A2 as shown below:



Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is C_{1-12}-alkyl, which may optionally be substituted by hydroxy, formyl, carboxy, carboxylic esters, amides or amines, C_{3-8} cycloalkyl, aryl, aralkyl; and wherein R^6 is hydrogen, halogen, CN, CF_3, NO_2, or OR', wherein R' is C_{1-4}-alkyl and R^5, R^7 and R^8 is hydrogen, provided R^6 is not CF_3, OCH_3, NO_2, CL or Br when R^1 is CH_3; or R^6 and R^7 independently are NO_2, halogen, CN, CF_3, or OR', wherein R' is C_{1-4}-alkyl and R^5 and R^8 are each hydrogen; or R^5 and R^6 together form a further fused aromatic ring, which may be substituted with halogen, NO_2, CN, CF_3 or OR', wherein R' is C_{1-4}-alkyl, and R^7 and R^8 independently are hydrogen, halogen, CN, CF_3, NO_2 or OR', wherein R' is C_{1-4}-alkyl; or R^7 and R^8 together form a further fused aromatic ring, which may be substituted with halogen, NO_2, CN, CF_3 or OR', wherein R' is C_{1-4}-alkyl, and R^5 and R^6 independently are hydrogen, halogen, CN, CF_3, NO_2 or OR', wherein R' is C_{1-4}-alkyl.

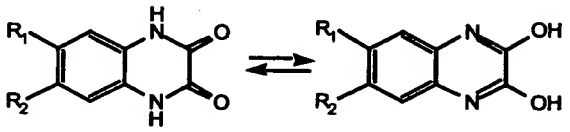
(55) Heterocyclic compounds in EP 0348 872 A1 as shown below:



Heterocyclic dihydroxyquinaoxaline compounds having the formula wherein R^1 and R^2 independently are hydrogen, NO_2, NH_2, CN, halogen, SO_2NH_2; -X-Y-Z- is selected from -N=N-NR^3-, -NR^3-N=N-, =N-NR^3-N=, -S-CH=N-, -N=CH-S_1 - CH=C(CO_2 R^3)-S-, -S-C(CO_2 R^3)= CH-, =N-Se-N=, -N-CR^3-NR^3-, -NR^3-CR^3=N-, =N-

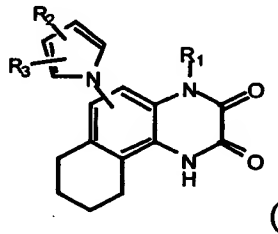
O-N=, -N=CR^3-CR^3=N-, -NH-CR^3=CR^3-CR^3 = N-, -N= CR^3-CR^3=CR^3-NH, =N-S-N=; wherein R^3 is hydrogen, lower alkyl, CF_3.

(56) Heterocyclic dihydroxyquinoxaline derivatives in US 4,812,458 as shown below:



Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is halogen, CN, CF_3, ethynyl, or N_3 and R^2 is SO_2C_{1-3}-alkyl, CF_3, NO_2, ethynyl, or CN.

(57) Pyrrolyl tetrahydrobenzoquinoxalinedione (I) in WO 96-11922 as shown below:

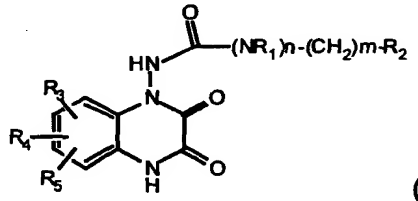


(I)

Pyrrolyl tetrahydrobenzoquinoxalinedione of formula I and their tautomeric and isomeric forms, as well as the pharmaceutically acceptable salts thereof, wherein R^1 hydrogen; an aliphatic residue with 1 to 6 C-atoms, which can carry one or two different substituents of the formula -$COOR^4$, -$CONHR^4$, -CO-R^4, -OR^4, -NHR^4, -NH-CO-R^4, -CONH-SO_2R^4 or $NHSO_2R^4$, of which R^4 means hydrogen, C_1-C_4-alkyl, phenyl, benzyl, 1-phenylethyl or 2-phenylethyl, wereby the phenyl rings in R^4 can be substituted by 1, 2 or 3 of the following substituents: C_1-C_4-alkyl, CF_3, C_1-C_4-alkoxy, F_3CO, halogen, nitro, CN, -OH, -$CONHR^5$ and/or -$COOR^5$ (R^5 hydrogen, C_1-C_4-alkyl, phenyl or benzyl); -O-R^6, of which R^6 is hydrogen or an aliphatic residue with up to 4 C-atoms which can carry one of the following residues: -$COOR^4$, -$CONHR^4$, -$NHCOR^4$, -$NHSO_2R^4$, -OH or phenyl; R^2 hydrogen, C_1-C_4-alkyl

or phenyl; R^3 hydrogen or the residue $-(CH_2)m-R^7$, whereby m is the number 0, 1, 2, 3 or 4 and R^7 hydrogen, C_1-C_4-alkyl, phenyl, phenylsulfonyl, NO_2, CN, $-COO-(CH_2)_n-R^8$, $-CONH-(CH_2)_n-R^8$, $-CONHSO_2R^4$, $-CO-R^8$, $-CH=CH-CONHR^8$, $-CH=CH-COOR^8$, $-CH=NOR^8$, $-CH_2-NR^8R^9$, $CH_2NH-CY-(CH_2)_nR^9$, $CH_2NH-CY-X-(CH_2)n-R^9$, $CH_2NH-CO-CF_3$, $CH_2NH-SO_2-R^9$ wereby X and Y independently of each other are oxygen or NH, n is the number 0, 1, 2, 3 or 4, R^8 means hydrogen or linear or branched C_1-C_4-alkyl, which can be substituted by one or two phenyl- or pyridyl-residues, and R^9 means hydrogen, linear or branched C_1-C_6-alkyl, phenyl or pyridyl, wereby all phenyl or pyridyl residues contained in R^8 and R^9 can carry one or two of the following residues: O-C_1-C_4-alkyl, F, Cl, Br, J, C_1-C_4-alkyl, NO_2, CF_3, $-COOR^5$, $-CONHR^5$, NH_2, CN, $-SO_2$phenyl, $-NHSO_2R^5$, $-NHCOR^5$, OH, $-SO_2-C_1-C_4$-alkyl, $-NHCOCF_3$, $-SO_2R^5$ and $-OCF_3$.

(58) Amido-quinoxalinedione (I) in WO 95-35289 as shown below:

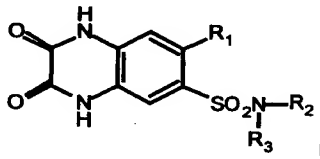


(I)

Amido-quinoxalinedione derivatives of formula (I), their tautomers, isomers and enantiomers, and their salts in which R^1 = H or 1-4C alkyl; n = 0-1; m = 0-4; R^2 = H, 1-6C alkyl or phenyl (optionally mono- or di-substituted with 1-4C alkyl, OR^6, NH_2, NO_2, $NHCOR^6$, CN, CF_3, OCF_3, CO_2R^6, F, Cl, Br, I, COR^6 or SO_2R^6); R3 = F, Cl, Br, I, 1-4C alkyl, OR^7, COR^7, NH_2, NO_2, $NHCOR^7$, CF_3, CN; R4, R5 = H, 1-4C alkyl, 1-4C alkoxy, CF_3, OCF_3, F, Br, I, NO_2, CN or an annellated benzene ring (optionally mono or di-substituted with up to 2 1-4C alkyl, 1-4C alkoxy, CF_3, OCF_3, F, Br, I, NO_2, CN); R^6 = H, 1-4C alkyl, phenyl or benzyl; R^7 = H, 1=4C alkyl or CF_3; R^8 = H, 1-4C alkyl, phenyl, phenylsulphonyl, NO_2, CN, $COO(CH_2)_rR$, $CONH(CH_2)_rR$, COR,

CH=CHCONHR, CH_2NRR', $CH_2NHCY(CH_2)_rR'$, CH=CHCOOR, CH=NOR, CH=NR, CH2NHCY-Z(CH2)rR', CH2NHCOCF3 or a gp. of formula (b)-(f); R9 = H or 1-4C alkyl; R = H , 1-4C alkyl, phenyl, benzyl, pyridyl or benzhydryl; R' = H, 1-4C alkyl, Ph, pyridyl or 4-(R-substituted)-piperidin-1-yl; Y = O or N; Z = O or NH; r = 0-4; q = 0-2; the benzene rings in R^8, R and R' are optionally mono- or di-substituted with NH_2, OMe, OEt, Cl, Br, OCF_3, F, Me, Et, NO_2, $COOR^1$, $CONHR^1$, CH_2NHR^1, $CH_2NHCOCF_3$, $CH_2NHCOMe$, $NHSO_2Me$, NHCOMe or $NHCOCF_3$.

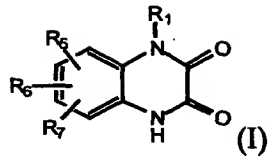
(59) Acid amide derivatives (I) in WO 95-31443 as shown below:



(I)

Acid amides of the formula wherein R^1 represents hydrogen or nitro, R^2 and R^3 stand, independently from each other, for hydrogen, lower alkyl or lower alkenyl optionally carrying a substituent selected from the group consisting of halogen, hydroxy, lower alkoxy, di(lower alkyl) amino, phenyl-lower alkoxycarbonyl and a 5- to 6-membered saturated hetero-ring containing 1 or 2 nitrogen and/or oxygen atom (s); or R^2 and R^3 form, together with the adjacent nitrogen atom, a 6-membered saturated heterocyclic group containing optionally 1 or 2 additional nitrogen atoms and/or oxygen atoms (s), said ring optionally carrying a hydroxy or a hydroxy-lower alkyl group; and all of the possible mesomers, tautomeric forms and stereoisomers of the acid amides of the formula (I) and the mixtures thereof.

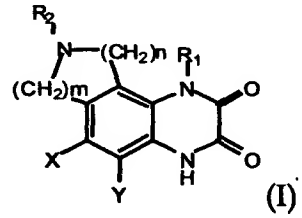
(60) Quinoxalindione derivatives (I) in WO 97-19066 as shown below:



(I)

Quinoxalindione derivatives of formula (I), their isomers and salts are new: R^1 = -$(CH_2)_n$-CR_2H-$(CH_2)_m$-Z; R^5 = 1-6C alkyl or 2-6C alkenyl (both optionally substituted by Q), SO_pR^{13} or -CH=R^{15}; Q = halo, OR^8, NR^9R^{10}, SO_oR^{11} or COR^{12}; or aryl or heteroaryl (both optionally substituted); R^6, R^7 = H, halo, NO_2, CN, $NR^{16}R^{17}$, COR^{14} or OR^{18}; or aryl or heteroaryl (both optionally substituted); 1-6C alkyl or 2-6C alkenyl (both optionally substituted by Q), SO_pR^{13} or -CH=R^{15}; R^2 = H or -$(CH_2)_qR^3$; R^3 = H, OH, 1-6C alkoxy or $NR^{19}R^{20}$; n, m, q = 0-3; Z = POXY, OPOXY, SO_2R^{21} $COOR^{22}$, CN or tetrazolyl; R^8, R^{18} = H or 1-6C alkyl (optionally halo substituted); o, p = 0-2; R^{11}, R^{13} = H, 1-6C alkyl or optionally substituted aryl; R^{12}, R^{14}, R^{21} = OH, 1-6C alkoxy or $NR^{23}R^{24}$; R^{15} = O, =NOH or a group of formula (a): X, Y = OH, 1-6C alkoxy, 1-4C alkyl or $NR^{25}R^{26}$; R^9 and R^{10}, R^{16} and R^{17}, R^{19} and R^{20}, R^{23} and R^{24}, R^{25} and R^{26} = H, 1-4C alkyl, aryl, or together with the N atom form a 5-7 membered saturated heterocycle (optionally containing an additional O, S or N and optionally substituted), or an unsaturated 5-membered heterocycle containing 1-3 N and optionally substituted; provided that R^5 is not CF_3 or Me.

(61) N-substituted fused azacycloalkylquinoxalinediones (I) in WO 96-28445 as shown below:

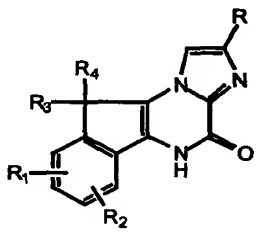


(I)

In formula (I) m and n are independently 0,1 or 2 provided that m + n is > 1. R^1 is hydrogen, an alkyl or an alkylaryl; X and Y are independently hydrogen, halogen, nitro, cyano, trifluoromethyl, COOH, $CONR^4R^5$, SO_2CF_3, SO_2R^4, $SONR^4$ R^5, alkyl, alkenyl, $(CH_2)_zCONR^4R^5$, $(CH_2)_zCOOR^4$, or $NHCOR^4$, wherein R^4 and R^5 are

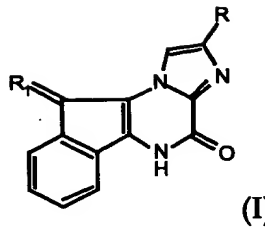
independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl or alkylaryl, and z is an integer from 0 to 4; R^2 is alky $COOR^3$, alkylamine, alkyquanidine, aryl, alkylaryl, COalkyl, COalkylaryl, $CONR^3$alkyl, $CONR^3$aryl, $CONR^3$alkylaryl, $CSNR^3$alkyl, $CSNR^3$alkylaryl or a common amino acid moiety joined by an amide bond, wherein R^3 is hydrogen, alkyl or alkylaryl.

(62) Spiro[heterocycle-imidazo[1,2-a]indeno[1,2-e]pyrazine]-4'-ones (I) in WO 96-14318 as shown below:



Compounds of formula (I), wherein R_3 and R_4, taken together with the carbon atom to which they are attached, form (a) a 2- or 3-pyrrolidine ring, a 2- or 4-piperidine ring or a 2-azacycloheptane ring, said rings being optionally substituted at the nitrogen atom by an alkyl radical, -CHO, $-COOR_{11}$, -CO-alk- $COOR_6$, -CO-alk-NR_6 R_{12} , -CO-alk-$CONR_6R_8$, -CO-$COOR_6$, -CO-CH_2-O-CH_2-$COOR_6$, -CO-CH_2-S-CH_2-$COOR_6$, -CO-alk, -CO-Ar^{11}. -CO-alk- Ar^{11}, -CO-NH-Ar^{11}, -CO-NH-alk-Ar^{11}, -CO-Het, -CO-alk-Het, -CO-NH-Het, -CO-NH-alk-Het, -CO-NH_2, -CO-NH-alk, -CO-N(alk)alk', -CS-NH_2, -CS-NH-alk, -CS-NH-Ar^{11}, -CS-NH-Het, -alk-Het, -alk- NR_6 R_8, -alk- Ar^{11}, -SO_2-alk, SO_2-Ar or -CO-cycloalkyl, where the cycloalkyl is optionally 2-substituted by a carboxy radical; or (b) a 2-pyrrolidine-5-one ring.

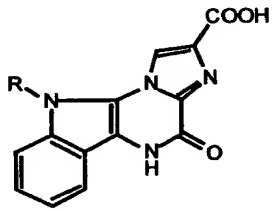
(63) 5H,10H-Imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives (I) in WO 97-25327 as shown below:



(I)

Compounds of formula (I), wherein R is a hydrogen atom or a -COOH or CH_2OH radical, R_1 is a -CH-R_2 radical, R_2 is a 3-dimethyl-1H-pyrazole-4-yl, 4-chloro-1-methylimidazole-5-yl or 3-hydroxy-isoxazole-5-yl radical except for 10-(1,3-dimethyl-1H-pyrazole-4-methylene)-5H, 10H-imidazo [1,2-a] indeno [1,2-e] pyrazine-4-one, isomers thereof, salts thereof, the preparation thereof and drugs containing said compounds.

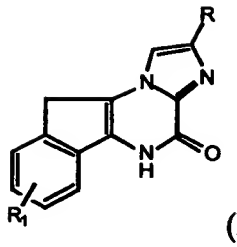
(64) 5H,10H-Imidazo[1,2-a]indolo[3,2-e]pyrazine-4-one derivatives (I) in WO 97-25329 as shown below:



(I)

Compounds of formula (I) wherein R is a hydrogen atom or an -alk-COOH radical, racemic mixtures, enantiomers and diastereoisomers thereof, salts thereof, the preparation thereof and drugs containing said compounds.

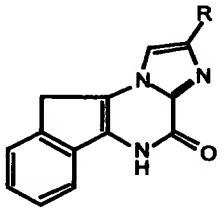
(65) 5H,10H-Imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives (I) in WO 97-25328 as shown below:



(I)

Compounds of formula (I), wherein R is a hydrogen atom or a -COOH, -alk-COOH, - PO_3H_2 , CH_2 -PO_3-H_2 or -CH=CH-COOH radical, or a phenyl radical substituted by a carboxy radical, R_1 is an alk-CN, -alk-COOH, alk-Het, alk- PO_3H_2 or -alk-CO-NH-SO_2R_2 radical, R_2 is an alkyl or phenyl radical, alk is an alkyl radical, Het is a saturated or unsaturated mono- or polycyclic heterocyclic ring containing 1-9 carbon atoms and one or more heteroatoms selected from O, S and N, said heterocyclic ring optionally being substituted by one or more alkyl, phenyl or phenylalkyl radicals, with the proviso that when R is a hydrogen atom or a -COOH or - PO_3H_2 radical, R_1 cannot be -alk-COOH, isomers, racemic, mixtures, enantiomers and diastereoisomers thereof, salts thereof, the preparation thereof, intermediates thereof and drugs containing said compounds.

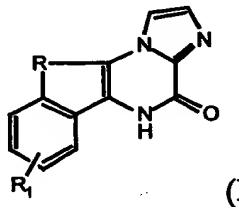
(66) 2-Substituted 5H,10H-imidazo[1,2-a]indeno[1,2-e]pyrazine-4-ones (I) in WO 97-25326 as shown below:



Compounds of formula (I), wherein R is a -CO-CH_2-PO_3H_2 , -CO-NH-tetrazole-5-yl, -CO-NHOH, CO-NH-NH_2 , -alk-COOH, -alk-COOalk', -CH_2-PO_3H_2, -CO-NH-SO_2-R_1 or -CH=CH-COOH radical, or a phenyl radical substituted by a carboxy radical, alk and alk' are an alkyl radical and R_1 is an alkyl, trifluoromethyl or phenyl radical optionally substituted by a carboxy or alkoxy-carbonyl radical, racemic mixtures,

isomers, enantiomers and diastereoisomers thereof, salts thereof, the preparation thereof and drugs containing said compounds.

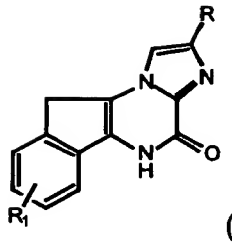
(67) Indeno[1,2-e]pyrazine-4-ones (I) in WO 97-10246 as shown below:



(I)

Compounds of formula (I), wherein R is a C=CH- R_2, C(R_3) R_4, CH- NH_2, CH-CH(OH)-COOH or CH-CH(OH)-COOalk radical, R_1 is an alk-NH_2 or alk-NH-CO-R_5 radical, R_2 is a -COOH or -COOalk radical, R_3 is an alkyl, -alk-Ar or -alk-Het radical, R_4 is an NH_2, -NH-alk, -N(alk)-alk', -NH-CO-alk, -NH-CO-Ar', -NH-CO-ALK-Ar', -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-COOH, -NH-CO-alk-COOalk', -alk-COOH, -alk-COOalk', -NH-CO-NH_2, -NH-CO-NH-alk or -NH-CO-NH-Ar' or -NH-CO-NH-alk-Ar' radical, or R_3 and R_4, together with the carbon atom to which they are attached, form a 2- or 3-pyrrolidine, 2- or 4-piperidine or 2-azacycloheptane substituted or unsubstituted ring, R_5 is an - NH_2, -NH-alk, -NH-Ar', -NH-cycloalkyl, -NH-alk-Ar' or -N(alk)-alk' radical, the salts thereof, the preparation thereof and medicaments containing same.

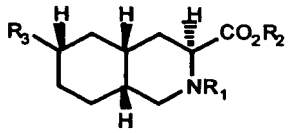
(68) 5H,10H-Imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives (I) in WO 96-31511 as shown below:



(I)

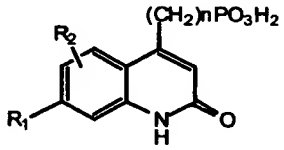
Compounds of formula (I), wherein R is a hydrogen atom or a carboxy, alkoxycarbonyl, -CO-NR_4 R_5, -PO_3H_2 or -CH_2 OH radical and R_1 is an alk-NH_2, -alk-NH-CO- R_3, -alk-$COOR_4$, -alk-CO-NR_5 R_6 or -CO-NH-R_7 radical.

(69) Decahydroisoquinoline compounds (I) in US 5,356,902 as shown below:



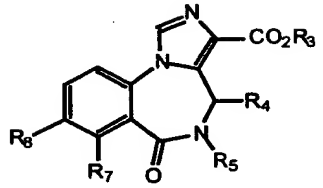
Compound of the formula (I) wherein: R^1 is hydrogen, C_{1-10} alkyl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl or acyl; R^2 is hydrogen, C_1 - C_6 alkyl, substituted alkyl cycloalkyl, or arylalkyl; R^3 is a group of the formula; R^4 is hydrogen, C_{1-4} alkyl, CF_3, phenyl, bromo, iodo, or chloro; or a pharmaceutically acceptable salt thereof.

(70) Phosphonoalkylquinolin-2-ones in US 5,342,946 as shown below:



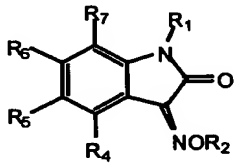
Having the general formula :wherein n is 0, 1, 2 or 3; R1 and R2 are selected from the group consisting of hydrogen, halogen, halomethyl, nitro, amino, alkoxy, hydroxyl, hydroxymethyl, C1 to C6 lower alkyl and C7 to C12 higher alkyl, aryl, and aralkyl; and the pharmaceutically acceptable salts thereof.

(71) Imidazobenzodiazepine compounds (I) in US 5,270,306 as shown below:



Compound having the formula : wherein R^3 is hydrogen, C_{1-8} -alkyl which may be branched, or cycloalkylmethyl; R^7 and R^8 are independently hydrogen, halogen, CF_3, CN, NO_2, NH_2, C_{1-4}-alkyl or C_{1-4} -alkoxy; and R^4 is hydrogen and R^5 is hydrogen or C_{1-7} alkyl; or R^4 and R^5 together signify $(CH_2)_n$ wherein n is an integer of 2-3.

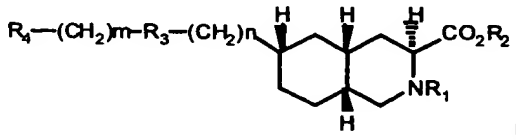
(72) Isatine derivatives in US 5,192,792 as shown below:



Indole-2,3-dione-3-oxime compound having the formula wherein R^1 is hydrogen, C_{1-6} -alkyl which may be branched, C_{3-7} -cyclo-alkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C_{1-6} -alkoxy, CH_2 CO_2 R'wherein R' is hydrogen or C_{1-6}-alkyl which may be branched, CH_2CN, CH_2CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C_{1-6} -alkyl, or $CH_2C(=NOH)NH_2$; R^2 is (1) alkenyl of from two to six carbon atoms, preferably allyl, (2) alkynyl of from two to six carbons, preferably propargyl, (3) $(CH_2)_{1-6}$ CO_2 H, (4) $(CH_2)_{1-6}$ CONHR wherein R is C_{1-6} alkyl, optionally branched; aryl which is phenyl optionally substituted by one or more of lower alkyl of from one to four carbons, halogen wherein halogen is

fluoro, chloro, bromo, or iodo, trifluromenthyl, cyano, carboxy, alkoxycarbonyl wherein the alkoxy is of from one to four carbons, alkylthio wherein the alkyl is of from one to four carbons, nitro, acyl of from two to four carbons, hydroxy, C_{1-6} -alkoxy, CH_2 CO_2 R′ wherein R′ is hydrogen or C_{1-6} -alkyl which may be branched, CH_2CN, CH_2CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C_{1-6} alkyl, optionally branched; aralkyl which is aryl as defined above attached through C_{1-4} alkyl, or SO_2 R^{10} wherein R^{10} is C_{1-6} alkyl, optionally branched; aryl which is phenyl optionally substituted by one or more of lower alkyl of from one to four carbons, halogen wherein halogen is fluoro, chloro, bromo, or iodo, trifluoromethyl, cyano, carboxy, alkoxycarbonyl wherein the alkoxy is of from one to four carbons, alkylthio wherein the alkyl is of from one to four carbons nitro, acyl of from two to four carbons, hydroxy, C_{1-6} alkoxy, CH_2 CO_2 R′ wherein R′ is hydrogen or C_{1-6} -alkyl which may be branched, CH_2CN, CH_2CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C_{1-6} alkyl, optionally branched; aralkyl which is aryl as defined above attached through C_{1-4} alkyl; R_4, R_5, R_6, R_7 independently are hydrogen, C_{1-6} alkyl, which may be branched, phenyl, halogen, C_{1-6} -alkoxy, NO_2, CN, CF_3, or $SO_2NR''R'''$ wherein R″ and R‴ independently are hydrogen, or C_{1-6} -alkyl; or R^6 and R^7 together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO_2, CF_3, CN, $SR_2NR''R'''$ wherein R″ and R‴ independently are hydrogen, or C_{1-6} -alkyl; and R^4 and R^5 have the meanings set forth above.

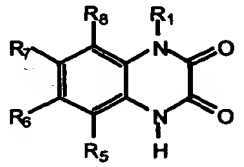
(73) Aryl-spaced decahydroisoquinoline-3-carboxylic acids in US 5,446,051:



(I)

Preferably, the compounds are of the general formula (I) wherein R^1 is H, C_{1}- C_{10} -alkyl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl, or acyl; R_2 is H, C_1 - C_6-alkyl, substituted alkyl, C_4- C_7 cycloalkyl or arylalkyl; R_3 is aryl, arylalkyl, heterocycle, substituted heterocycle, C_4- C_7 cycloalkyl or C_4- C_7 cycloalkenyl; R_4 is CO_2H, SO_3H, PO_3H_2, or one of the following cyclic compounds : wherein R^5 is H, C_{1-6} -alkyl or aryl; m = 0, 1 or 2; and n = 0, 1 or 2; or a pharmaceutically acceptable salt thereof.

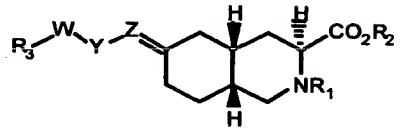
(74) Quinoxalindione derivatives reported in WO 94-25469 and shown below:



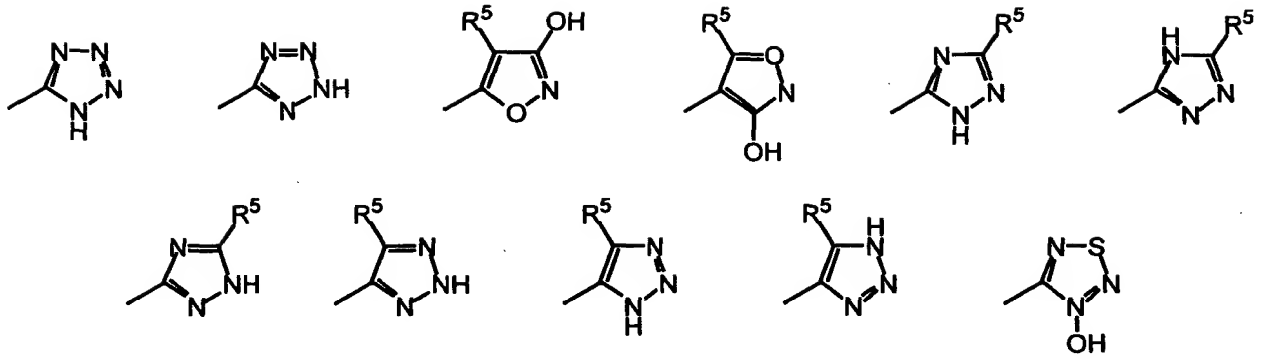
Quinoxalindione derivatives represented by the above formula wherein R1 is $(CH_2)_n$-CR2H-$(CH_2)_m$-Z and R5, R6, R7 and R8 together or independently are hydrogen, C1-C6 alkyl, CF_3, nitro, halogen, NR9R10, cyano, SO_pR11, $SO_2NR12R13$, SO_3H, SO_3C_{1-6}-alkyl or OR14; R2 is hydrogen, or $(CH_2)_q$-R3; R3 is hydrogen, OH, C_{1-6}-alkoxy or NR15R16, and n, m and q are 0,1,2, or 3; Z is POXY, OPOXY, OR17, NR18R19, NH-COR20, NH-SO_2R21, SO_2R22, CO_2R23, halogen, cyano or tetrazole; R11 is hydrogen, C1-C6 alkyl, phenyl; p is 0, 1, or 2; R12, R13, R17 or R23 is hydrogen or C1-C4 alkyl; R14 is hydrogen or 1-3 halogen substituted C1-C6 alkyl; R20 and R21 are C1-C6 alkyl or halogen substituted phenyl or hetaryl; R22 is OH, C1-C6 alkoxy or NR24R25; X and Y are together or independently OH, C1-C6 alkoxy, C1-C4 alkyl or NR18R19; R9 and R10 are together or independently hydrogen, CO-C1-C6 alkyl, phenyl or C1-C6 alkyl, which may be substituted with C1-C4 alkoxy or C1-C4 alkyl mono- or disubstituted NH_2 group, or together with the nitrogen form a 5-7 membered heterocyclic ring which may contain additional N, S or O and can be substituted, or form five membered heterocyclic ring which may contain 1-3 nitrogens and can be substituted; R15 and R16, R18 and R19 together or independently are hydrogen, C1-C4 alkyl, phenyl or together with the

oxygen form 5-7 membered heterocyclic ring which may contain additional N, S or O and can be substituted, or form five membered heterocyclic ring which may contain 1-3 nitrogens and can be substituted; R24 and R25 together or independently are hydrogen, C1-C4 alkyl, or together with the oxygen form 5-7 membered heterocyclic ring which may contain additional N, S or O, and their isomers and salts and provided R2 is hydrogen and Z POXY or CO_2R23 then R5-R8 is not hydrogen; and provided R2 is hydrogen, Z POXY or CO_2R23 and R5, R6, R7 and R8 are CF_3, NO_2, halogen, NH_2 or methyl, the compounds of the above formula are double-substituted and provided R1 is methanophosphonic acid and R6 cyano or substituted imidazole then together R5, R7 and R8 is not hydrogen and provided R1 is methanosulphonic acid and R6 is CF_3 or NO_2 and R7 is imidazole, R5 and R8 is not hydrogen; and provided R1 is CH_2-COOH and R5 and R8 is hydrogen, R6 and R7 is not halogen or methyl; and the pharmaceutically acceptable salts thereof.

(75) Isoquinolinyl-carboxylic acid compounds reported in US 5,606,062 and shown below:

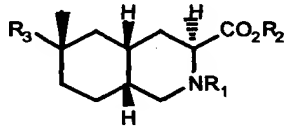


Isoquinolinyl-carboxylic acid compounds represented by the above formula wherein R1 is hydrogen, C1-C10 alkyl, arylalkyl, alkoxycarbonyl, or acyl; R2 is hydrogen, C1-C6 alkyl, substituted alkyl, cycloalkyl, or arylalkyl; R3 is CO_2H, SO_3H, $CONHSO_2R8$, or a group of formula:

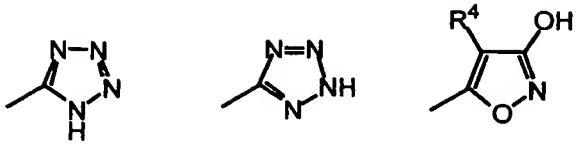


W is $(CH_2)_n$, S, SO, SO_2; Y is CHR7, NR4, O, S, SO, or SO_2; Z is NR6, CHR7, or CH; or W and Y together are HC=CH or C≡C, or Y and Z together are HC=CH or C≡C; R4 is hydrogen, C1-C4 alkyl, phenyl, or acyl; R5 is hydrogen, C1-C4 alkyl, CF_3, phenyl, hydroxy, amino, bromo, iodo, or chloro; R6 is acyl; R7 is independently hydrogen, C1-C4 alkyl, phenyl, or substituted phenyl; R8 is C1-C4 alkyl or tetrazole-5-yl; and n is 0, 1, or 2; provided that when Y is NR4, O, S, SO, or SO_2, W is $(CH_2)_n$ and Z is CHR7 or CH; further provided that when W is S, SO, or SO_2, Y is CHR7, Z is CHR7 or CH or Y and Z together are HC=CH or C≡C; further provided that when W and Z are CH_2, Y is not S; further provided that when W and Y together are HC=CH or C≡C, Z is CHR7; and the pharmaceutically acceptable salts thereof.

(76) Decahydroisoquinoline compounds described in US 5,527,810 as shown below:

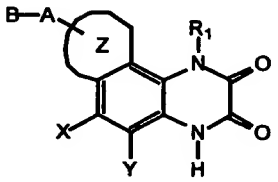


Decahydroisoquinoline represented by the above formula wherein R1 is hydrogen, C1-C10 alkyl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl or acyl; R2 is hydrogen, C1-C6 alkyl, substituted alkyl, cycloalkyl, or arylalkyl; R3 is a group of the formula:



R4 is hydrogen, C1-C4 alkyl, CF_3, phenyl, bromo, iodo, or chloro, and the pharmaceutically acceptable salts thereof.

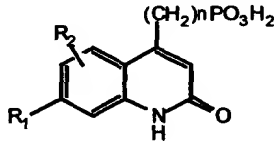
(77) Cycloalkynoxalinediones shown in US 5,721,234 as exemplified below:



Cycloalkynoxalinediones represented by the above formula wherein Z is an alicyclic fused ring having 5 to 7 carbon atoms; R1 is hydrogen, an alkyl or an arylalkyl; X and Y are independently hydrogen, halogen, nitro, cyano, COOH, CONR2R3, SONR2R3 wherein R2 and R3 are independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl or aralkyl; and A is O, CH_2, NR4, CH_2NR4, CN, tetrazole or CO wherein R4 is hydrogen, alkyl, hydroxyalkyl, aminoalkylamine or aralkyl, wherein (i) when A is O, CH_2, NR4, or CH_2NR4 then B is hydrogen, alkyl, alkenyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aminoalkyl, heterocyclic, alkylheterocyclic, heterocyclic-methyl, heterocyclic-ethyl, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclic-carbonyl, alkylheterocyclic-carbonyl, any of which may be unsubstituted or substituted by one or more hydroxy, CO_2H, mercapto, amino, alkyl or butoxycarbonyl group, CONR5R6 wherein R5 is hydrogen, alkyl having 1 to 6 carbon atoms, or aralkyl, and R6 is alkyl, aryl, or aralkyl, or N, R5, and R6 taken together form a cyclic amine, or when A is NR4 or CH_2NR4 then B is a common amino acid moiety joined by an

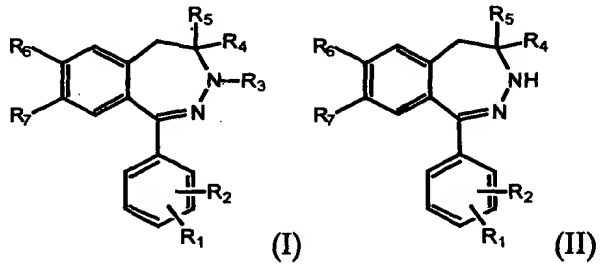
amide bond or B joins with R4 and the nitrogen to form a four to seven membered heterocyclic ring, provided that when Z is a fused cyclohexyl ring and R4 is hydrogen then B is not hydrogen; (ii) when A is CN then B is not present and Z is not a fused cyclohexyl ring; (iii) when A is tetrazole then B is hydrogen or alkyl having 1 to 6 carbon atoms; and (iv) when A is CO then B is hydroxy, alkoxy, aralkoxy, alkyl having 1 to 6 carbon atoms, aralkyl, NR7R8 wherein R7 is hydrogen, alkyl having 1 to 6 carbon atoms, or aralkyl, and R8 is alkyl, aryl, or aralkyl, or N, R7, and R8 taken together from a cyclic amine, and the pharmaceutically acceptable salts thereof.

(78) Phosphonoalkylquinolin-2-ones as reported in US 5,510,338 and shown below:



Phosphonoalkylquinolin-2-ones represented by the above formula wherein n is 0, 1, 2 or 3. R1 or R2 are selected from the group consisting of hydrogen, halogen, halomethyl, nitro, amino, alkoxy, hydroxyl, hydroxymethyl, C1 to C6 lover alkyl and C7 to C12 higher alkyl, aryl, and aralkyl; and the pharmaceutically acceptable salts thereof.

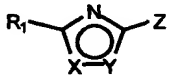
(79) 2,3-Benzodiazepine derivatives (I) and (II) in P 97 00688 as shown below:



2,3-Benzodiazepine derivatives and medicinal preparations containing such drugs represented by the formula I wherein R1 and R2 can be, independently from each other, hydrogen, halogen, alkyl group with 1-4 carbonic atoms, alcoxy group with 1-4 carbonic atoms, nitro group, trifluoromethyl group, or group having a general structure of -NR8R9, where the meaning of R8 and R9, can be, independently from each other, hydrogen, alkyl group with 1-4 carbonic atoms, or group having a general structure of -COR_{10}, where R10 means hydrogen atom, alkyl group with 1-6 carbonic atoms substituted in given cases, aryl group with 6-10 carbonic atoms, alcoxy group with 1-4 carbonic atoms, cycloalkyl group with 3-5 carbonic atoms, alkenyl group with 2-6 carbonic atoms, cycloalcoxy group with 3-5 carbonic atoms, or group having a general structure of -NR11R12, where the meaning of R11 and R12, independently from each other, hydrogen atom, alkyl group with 1-4 carbonic atoms, cycloalkyl group with 3-5 carbonic atoms, or aryl group with 6-10 carbonic atoms, the meaning of R3 can be alkyl group with 1-4 carbonic atoms, cycloalkyl group with 3-5 carbonic atoms, or group having a general structure of -CO-R13, where the meaning of R13 can be the same as given for R10, the meaning of R4 and R5, can be, independently from each other, hydrogen atom, or alkyl group with 1-3 carbonic atoms, the meaning of R6 and R7, can be, independently from each other, hydrogen atom, Cl atom, or Br atom, with the condition that if any of R4 or R5 means hydrogen atom, the second can only be other than hydrogen atom, further, the isomers, salts obtained with acid addition, and the medicinal preparations originating from them.

2,3-Benzodiazepine derivatives represented by the formula II wherein R1, R2, R4, R5, R6 and R7 is given for general structure (I).

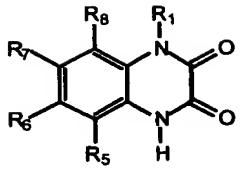
(80) Oxadiazole derivatives (I) in DE 196 43 037 A1 as shown below:



Oxadiazole derivatives of formula (I), and their racemates, enantiomers, diastereomers, mixtures and acid addition salts, are new. One of X, Y = N and the other = O; Z = pyridyl substituted by S1, or Ar (optionally substituted by R^2 and R^3); Ar = phenyl substituted at the 2-position by S1 and optionally at the 6-position by S2; or Ar = phenyl substituted at the 3- or 4- position by S2; S1 = B-V-D-R4, B-N(D-R^4)D-R^{41} or a group of formula (a) (optionally substituted by halo, oxo, OR7, OCOR7, 1-4C alkyl, 2-6C alkenyl or 2-6C alkynyl); S2 = B-V-D-R^4 or B-N(D-R^4)D-R^{41}; V, E = O, S or NR^7; D = 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene (all optionally substituted by Q1); B = bond or as for D; n, m = 1-3, and n+m is at least 2; R^1 = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by one or more Q2), a norbornane, norbornene, di(3-6C)cycloalkyl-methyl, adamantane or noradamantane residue (all optionally substituted by 1-4C alkyl), H, phenyl (optionally substituted by 1-3 Q3 (directly or via 1-4C alkylene)), phenyl (substituted by B-N(D-R^4)DR^{41}, B-V-D-R^4, OCH_2O or OCH_2CH_2O), A''-A', 3-7C cycloalkyl (optionally substituted by Q2), fluorenyl, a [3.3.0]bicyclooctane group; or an optionally substituted group of formula (b)-(d); y = 1 or 2; z = 0-2; R^2, R^3 = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by Q2), SH, NR^5R^6, halo, NO_2, CF_3, OR^7, SR^7, $COOR^7$, 6-10C aryl, aryl(1-6C)alkyl or 6-10C aryloxy; or R^2+R^3 complete an unsaturated fused 5-7 membered ring (optionally containing one or more heteroatoms, and optionally substituted by OR^7, NR^5R^6, halo, CN, NO_2, CF_3, $COOR^7$, 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl; R^4, R^{41} = 1-10C alkoxy, 2-10C alkenyloxy or 2-10C alkynyloxy (all optionally substituted by Q2), OH, halo, NO_2, CF_3, CN, SH, 1-6C alkylmercapto, A-Ar', OAr', Ar'-substituted 1-6C alkoxy, M', NR^5R^6 or 3-8C cycloalkoxy (optionally substituted by oxo, OR^7 or $OCOR^7$); R^5, R^6 = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by OH, optionally substituted phenyl, optionally substituted benzyl, NR^7R^{71} or 1-8C alkoxy), H, optionally substituted 3-6C cycloalkyl or 6-10C aryl (optionally substituted by halo, OR^7, 1-4C alkyl, NR^7R^{71}, SO_3H or $COOR^7$); or

NR^5R^6 = an optionally unsaturated 5-6 membered ring, optionally containing other heteroatoms, and optionally substituted by Q4; R^7, R^{71} = H, R, 2-4C alkenyl, 2-4C alkynyl, or benzyl or phenyl (both optionally substituted by OH, Cl, Br or OMe); R^8 = 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, phenyl, benzyl or 3-6C cycloalkyl; R^9 = H, 1-4C alkyl, $COOR^7$, CH_2OR^7, $CONR^5R^6$ or phenyl; Q1 = CN, CHO, $COOR^7$, $CONHSO_2R^7$, $CONR^5R^6$, $CH=NOR^7$, COR^8, $CH(OR^7)R^8$, $CH(OR^7)OR^{71}$, $CH=CHR^9$, NR^5R^6, $NHCOR^7$, $NHCONR^5R^6$, $NHCOOR^7$, OR^7, $OCOR^7$, $OCOOR^7$, $OCONR^5R^6$, SR^7, SOR^7, SO_2R^7, SO_3H, $SO_2NR^5R^6$, halo, 1,3-dioxolan or 1,3-dioxan); Q2 = oxo or Q1; A" = 1-6C-alkyl, 2-6C alkenyl or 2-6C alkynyl; A = H or as for A"; A' = phenyl (optionally ring substituted, directly or via a 1-4C alkylene bridge, by one or more groups Q3), 3-7C cycloalkyl (optionally ring substituted, directly or via a 1-4C alkylene bridge, by one or more groups Q2), M, CONHM or NHCOM; Ar' = aryl substituted by one or more Q3; M' = 5-7 membered heterocycle linked via C, containing one or more heteroatoms, optionally substituted by benzyl, 1-4C alkyl, halo, OR^7, CN, NO_2, NH_2, $CH_2NR^5R^6$, OH, oxo, ketal, ethylene ketal, COOH, SO_3H, $COOR^7$, $CONR^5R^6$, COR^8, SO_2R^7 or $CONR^5R^6$ (sic)); M = heterocycle as for M', (which may also be linked by N, and also be substituted by optionally substituted phenyl or substituted benzyl); Q3 = halo, 1-4C alkyl, CF_3, CHO, $COOR^7$, $CONHSO_2R^7$, $CONR^5R^6$, $CH=NOR^7$, COR^8, $CH(OH)R^8$, $CH(OR^7)OR^{71}$, $CH=CHR^9$, NR^5R^6, NO_2, 1-4C alkyl-NR^5R^6, $NHCOR^7$, $NHCONR^5R^6$, $NHCOOR^7$, $NH\text{-}SO_2R^7$, OR^7, $OCOR^7$, $OCONR^5R^6$, SR^7, SOR^7, SO_2R^7, SO_3H or $SO_2NR^5R^6$; Q4 = 1-4C alkyl, (CH_2)n-Q5, halo, OR^7, CN, NO_2, NR^7R^7, SO_3H, $COOR^7$, $CONR^7R^{71}$, SO_2R^7, oxo or a ketal; Q5 = phenyl, NH_2, 1-4C alkylamino, di(1-8C)alkylamino or $NHCOOR^7$; heteroatoms = N, O, S.

(81) Quinoxalindione derivatives reported in WO 96-37500 and shown below:



Quinoxalindione derivatives represented by the formula I wherein R1 is -$(CH_2)_nCR^2H$-$(CH_2)_m$-Z and R^5, R^6, R^7 and R^8 together or independently are hydrogen, C_{1-6}-alkyl in which one or more hydrogen atoms are replaced with halogen atoms, nitro, halogen, NR^9R^{10}, cyano, SO_pR^{11}, $SO_2NR^{12}R^{13}$, SO_3H, SO_3C_{1-6}-alkyl or OR^{14}; R^2 hydrogen or $(CH_2)_q$-R^3; R3 hyrdogen, hydroxy, C_{1-6}-alkoxy or $NR^{15}R^{16}$; n, m and q can be 0, 1, 2 or 3; Z is POXY, OPOXY, SO_2R^{17}, COR^{18}, halogen, cyano or tetrazole; R^{11} H, C_{1-6}-alkyl, phenyl; p 0, 1 or 2; R^{12} and R^{13} are independently hydrogen or C_{1-4}-alkyl; R^{14} A-R^{19}, or means C_{6-12}-aryl- or hetaryl, which can be substituted with halogen, C_{1-6}-alkoxy, hydroxy, cyano, $NR^{20}R^{21}$, eventually with halogen substituted C_{1-6}-alkyl and/or COR^{22} and A linear or branched, saturated or unsaturated alkyls with C_{1-20}-carbon atoms in which one or several carbons can be substituted by O, S and/or NR^{26} and can besubstituted with halogen; and R^{19} hydrogen, $NR^{24}R^{25}$, halogen, C_{1-6}-alkyl, which eventually is substituted with halogen, C_{1-6}-alkoxy, COR^{23}, CN or one C_{6-12}-aryl or hetaryl which is substituted with halogen, and/or substituted COR^{22}; and R^{18} hydrogen, C_{1-4}-alkyl, hydroxy, C_{1-6}-alkoxy or $NR^{27}R^{28}$; R^{17}, R^{22} and R^{23} hydroxy, C_{1-6}-alkoxy or $NR^{29}R^{30}$, R^{26} hydrogen, C_{1-6}-alkyl, C_{1-6}-alkenyl, X and Y are similar or different and are hydroxy, C_{1-6}-alkoxy, C_{1-4}-alkyl or $NR^{27}R^{28}$; R^9 and R^{10}, R^{20} and R^{21} and/or R^{25} and R^{24}, are similar or different and hydrogen, CO-C_{1-6}-alkyl, phenyl or C_{1-6}-alkyl, which with C_{1-4}-alkoxy or one eventually with C_{1-4}-alkyl mono- or di-substituted aminogroup substituted is, or together with nitrogen atom bild 5-7-membered saturated heterocyclic ring, which may contain additional N, S- or O-atom and can be substituted, or bild 5-membered saturated heterocyclic ring, which contains 1-3 N atoms and can be substituted; R^{15} and R^{16}, R^{27} and R^{28}, R^{29} and R^{30} are similar or different and are hydrogen, C_{1-4}-alkyl, phenyl or bild together with nitrogen atom 5-7-membered saturated heterocyclic ring, which may contain additional O-, S-, N-

atom and can be substituted or bild 5-membered saturated heterocyclic ring, which can contain 1-3 nitrogen atoms and can be substituted, although R^5-R^8 always mean OR^{14}, and R^{14} does not mean H or eventuall 1-3 halogen substituted C_{1-6}-alkyl.

AMPA receptor channel blockers

The inhibitors of the present invention also include AMPA receptor channel blockers. The term "AMPA receptor channel blockers" is used to refer to moieties that reduce the permeability of channels associated with the AMPA receptor to cations (preferably to Na^+, K^+ and/or Ca^{2+} ions). AMPA receptor channel blockers can therefore be used to prevent a signal being transmitted due to ionic flux that would otherwise occur when glutamate binds to the AMPA receptor.

AMPA receptor channel blockers include e.g. fluorowillardiine and Joro spider toxin.

Having described the inhibitors of the present invention, their therapeutic uses will now be discussed in greater detail.

Therapeutic uses

Inhibitors of the present invention may be used in human and veterinary medicine. Treatments may be prophylactic or may be in respect of existing conditions.

As explained supra, the inhibitors may be used in the manufacture of a medicament for treating a demyelinating disorder. The term "demyelinating disorder" is used herein to include any disorder that results in a reduced level of myelination.

Demylinating disorders include acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV- and HTLV-myelopathy, and progressive multifocal leucoencephalopathy.

Demylinating disorders also include secondary demyelinating disorders - i.e. where bystander myelin loss occurs as a consequence of a secondary pathological insult.

Examples of secondary demyelinating disorders are CNS lupus erythematodes, polyarteriitis nodosa, Sjögren syndrome, sarcoidosis and isolated cerebral vasulitis.

The present invention includes within its scope pharmaceutically acceptable compositions useful in treating demyelinating disorders which comprise an inhibitor of the present invention. The inhibitor will usually be provided in combination with a pharmaceutically acceptable carrier. It may be used in any suitable form, provided that it can still act in inhibiting the interaction of glutamate with the AMPA receptor complex. For example, pharmaceutically acceptable salts, esters, hydrates, etc. may often be used.

Pharmaceutical compositions within the scope of the present invention may include one or more of the following: preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odourants, salts, buffers, coating agents or antioxidants.

They may contain a further therapeutically active agent in addition to an inhibitor of the present invention. The further therapeutically active agent may be an immunosuppresive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte

adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1) a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs) or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

The combination of an inhibitor of the present invention and a further therapeutically active agent may be used simultaneously, seperately or sequentially to treat a demyelinating disorder. It may provide synergistically effective combination. The further therapeutically active agent may be an immunosuppresive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1) a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs) or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

A pharmaceutical composition within the scope of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) routes. Such a composition may be prepared by any method known in the art of pharmacy, for example by admixing one or more active ingredients with a suitable carrier. Preferably it will be provided in unit dosage form. It will normally be provided in a sealed, sterile container e.g. in an an ampoule, a vial, a bottle, a blister pack, etc.

Different drug delivery systems can be used to administer pharmaceutical compositions of the present invention, depending upon the desired route of administration. Such systems

include tablets, capsules, lozenges, pastilles, powders, solutions, suspensions, syrups, ointments, pastes, oils, aerosols, suppositories, enemas, pessaries, tampons, sprays, nebulizers, injectable compositions, etc.

Dosages of the inhibitors of the present invention can vary between wide limits, depending upon the nature of the treatment and the age and condition of the individual to be treated. However, a daily dosage of from 0.5 mg to 1000 mg, preferably of from 50-200 mg may be suitable. The dosage may be repeated as often as appropriate. If side-effects develop, the amount and/or frequency of the dosage can be reduced, in accordance with good clinical practice.

The present invention will now be described by way of example only, with reference to the accompanying drawings, wherein:

FIGURE 1 shows that the AMPA receptor antagonist NBQX reduces severity of paralysis during EAE in rats. NBQX (30mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represent the mean ± SEM of disease score (n=10/group).

FIGURE 2 shows that NBQX (30mg/kg i.p. twice daily; 10-16 dpi) reduces weight loss during the course of EAE in rats prior to cessation of treatment (16 dpi). Data represent the mean ± SEM of disease score (n=10/group).

EXAMPLES

Experimental allergic encephalomyelitis (EAE), an inducible autoimmune disease, represents the best characterized animal model of a demyelinating disorder and drugs active in this model proved to be active in humans (Pender MP (1996). Experimental autoimmune encephalomyelitis, In Autoimmune Neurological Disease, Editors Pender MP and McCombe PA, Cambridge University Press. pp 26-88).

Here we describe a surprising observation on the reduction in neurological deficits during acute EAE in rats following treatment with a non-immunomodulatory and non-antiinflamatory agent, the AMPA receptor antagonist, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo-(F)-quinoxaline (NBQX).

Animals

Female Lewis rats (205 + 10 g) obtained from Charles River, Kent, UK, were housed in pairs under environmentally controlled conditions (6:00 a.m. - 6:00 p.m. light/dark cycle; 22-24°C; 45-55% humidity) and allowed free access to food and water. Experimental groups consisted of 10 animals.

Induction of Acute-Active EAE in Lewis Rats

Rats were immunised in each hind foot with 50 µl of inoculum containing 50 µg guinea pig myelin basic protein (MBP, prepared by the method of Dunkley and Carnegie (1974); final concentration 2 mg/ml), emulsified in Freund's complete adjuvant (CFA; Sigma, UK) containing Mycobacterium tuberculosis H37Ra (final concentration 5.5 mg/ml; Difco Laboratories, UK).

Assessment of Clinical EAE in Lewis rats

Animals were weighed and monitored daily and clinical disease scored as (0) no clinical signs; (1) flaccid tail and weight loss; (2) hind limb hypotonia with further weight loss; (3) complete hind limb paralysis; (4) paraplegia and (5) death. In addition, intermediate scores

were assigned to animals which showed a loss of tonicity in the distal half of the tail (score = 0.5), paralysis of one hind limb (score = 2.5) or complete hind limb paralysis with forelimb weakness (score = 3.5). During the period of compound administration (10-16 days post immunisation; dpi) animals were scored 15h after injection of vehicle or NBQX to avoid any acute effect of treatment on disease score.

NBQX administration regime

NBQX was initially dissolved in NaOH and diluted with water. pH was adjusted with HCl. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or NBQX in the dose of 30mg/kg.

Results

Effect of NBQX on disease progression during EAE in the Lewis rat

Following immunisation with MBP, neurological deficit developed in 10/10 vehicle treated animals, 8 of which displayed paralysis of one or both hind limbs; the mean disease onset and duration were 11.8 dpi and 4.7 dpi respectively (Figure 1 and Table 1). Twice daily treatment from day 10 to 16 post immunisation with NBQX completely prevented the development of paralysis in 6 out of 10 rats, whilst one animal exhibited loss of tone in the most proximal part of the tail (score 0.25) for one day only. The remaining 3 rats displayed paresis of score 1, 2.5 and 3, the onset and duration of which were similar to vehicle injected animals. Thus NBQX significantly reduced disease duration ($p<0.001$), and peak and cumulative disease score ($p<0.01$) relative to vehicle treatment. NBQX also conferred protection on weight loss, significantly delaying the onset until 13 dpi ($p<0.01$) and decreasing the percent body weight lost at the cessation of NBQX administration (day 16; Figure 2 and Table 1).

Table 1. Parameters of disease activity during Lewis rat acute EAE

Treatment	Incidence (%)	[a]Onset (d.p.i.)	Duration (days)	Peak Disease Score	[b]Cumulative Disease Score	[c]Weight Loss (%)
Vehicle	10/10 (100)	11.8 (11-14)	4.7 (4-5)	2.7 (2-3.25)	9.8 (5.5-13)	18 (12-23)
NBQX	4/10 (75)	11.8 (11-12)	1.5 (0-5)††	0.7 (0-3)†	2.4 (0-11.5)†	14 (5-20)*

Values in the table represent the mean and range where n=10; *$p<0.05$, $p<0.01$ and $p<0.001$ vs vehicle, Student t-test or Mann-Whitney U-test for parametric and non-parametric data respectively. a; n=4 for NBQX. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on cessation of treatment (16 dpi) expressed as a percent of the maximum weight before disease onset.

General remarks

The foregoing description of the invention is merely illustrative thereof and it should therefore be appreciated that various variations and modifications can be made without departing from the spirit or scope of the invention as set forth in the accompanying claims.

Where preferred or optional features are described in connection with particular aspects of the present invention, they shall be deemed to apply *mutatis mutandis* to other aspects of the invention unless the context indicates otherwise.

All documents cited herein are hereby incorporated by reference, as are any citations referred to in said documents.

CLAIMS

1. The use of an inhibitor of the interaction of glutamate with the AMPA receptor complex in the manufacture of a medicament for treating a demyelinating disorder.

2. The use according to claim 1, wherein the demyelinating disorder is acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV- or HTLV-myelopathy, progressive multifocal leucoencephalopathy, or a secondary demyelinating disorder.

3. The use according to claim 2, wherein the secondary demyelinating disorder is CNS lupus erythematodes, polyarteriitis nodosa, Sjögren syndrome, sarcoidosis or isolated cerebral vasulitis.

4 The use according to any preceding claim wherein the inhibitor is an antagonist of the binding of glutamate to the AMPA receptor.

5. The use according to any preceding claim, wherein the inhibitor is an L-glutamate derivative, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate drivative, arylthioxaline (42), acid amide (59), hydrazone (48), quinoline (51), quinolinone (70,78), quinoxaline (8,9,13,14,15,17,20,47,50,52,53,54,55,56), quinoxalinedione (7,11,23,43,57,58,60,61,74,77,81), triazoloquinoxalinedione (3,4,5), pyrrolylquinoxalindione (6), quinazolinone (22), quinazolinedione (35), quinoxalinone (29), phenylpyridazinoindoledione (41), indenopyrazinone (24,32,63,65,66,67,68), imidazoloquinoxalinone (12), indolo-pyrazinone (64), imidazo-pyrazinone (31,33,34,37,44,62), triazolo-pyrazinone (30), benzothiadiazine (16,36), 4-hydroxypyrrolone, pyrrolo-pyridazinone (40), phthalazine (25), quinolone (18,19), amino-alkanoic acid (1), isatine (72), phenyl-azolophthalazine, amino- or desamino- 2,3-

benzodiazepine (10,26,27,28,38,49,79), 2,3-benzodiazepin-4-one (21), imidazobenzodiazepine (71), β-carboline-3-carboxylic acid, alkoxy-phenyl-benzodiazepine, isoquinolinyl-carboxylic acid derivatives (75), acetyl-aminophenyl-dihydro-methyl-dioxolo-benzodiazepine, pyrimidinone (46), oxadiazol (80), isatinoxime, decahydroisoquinoline (69,73,76), piperazine derivative (2), tetramic acid derivatives (39), or a sulphamate. (The reference numbers used above correspond with the numbers used in the list of antagonists provided in the description.)

6. The use according to any of claims 1 to 4, wherein the inhibitor is L-glutamic acid diethylester, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX), 6,7-dinitro-quinoxaline-2,3-dione (DNQX), 6-nitro-7-cyano-quinoxaline-2,3-dione (CNQX), 6-(1-imidazolyl)-7-nitro-quinoxaline-2,3(1H,4H)-dione (YM90K), (3RS,4aRS,6RS,8aRS)-6-(2-(1H-tetrazole-5-yl)ethyl)-decahydroiso-quinoline-3-carboxylic acid (LY293558), 9-methyl-amino-6-nitro-hexahydro-benzo(F) quinoxalinedione (PNQX), 8-methyl-5-(4-(N,N-dimethylsulphamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2h]-isoquinoline-2,3-dione-3-O-(3-hydroxybutyric acid-2-yl)oxime (NS 1209), 6,7-dichloro-2-(1H)-quinolinone-3-phosphonate (S 17625-2), and [1,2,3,4-tetrahydro-7-morpholinyl-2,3-dioxo-6-(trifluoromethyl)quinoxalin-1-yl]methyl-phosphonate (ZK200775), 1-(4-aminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine (GYKI52466), topiramate and 5-{2-[2-(N,N-dimethylamino)ethyl]oxy-phenyl}-3-phenyl-1,2,4-oxadiazol.

7. The use according to any of claims 1 to 3, wherein the inhibitor is an AMPA receptor channel blocker.

8. The use according to claim, wherein the AMPA receptor channel blocker is fluorowillardiine or Joro spider toxin.

9. The use according to any preceding claim wherein the inhibitor is combined with one or more of: an immunosuppresive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-

beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1) a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs) or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

10. A pharmaceutical composition comprising an inhibitor as described in any of claims 1 to 9 and a pharmaceutically acceptable carrier.

11. A combined preparation of an inhibitor as decribed in any claims 1 to 10 and one or more of: an immunosuppresive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1) a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs) or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein) for simultaneous, separate or sequential use in the treatment of a demyelinating disorder.

12. The invention substantially as hereinbefore described.

ABSTRACT

Pharmaceutical Compositions And Their Uses

New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the AMPA receptor complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compositions.

FIGURE 1

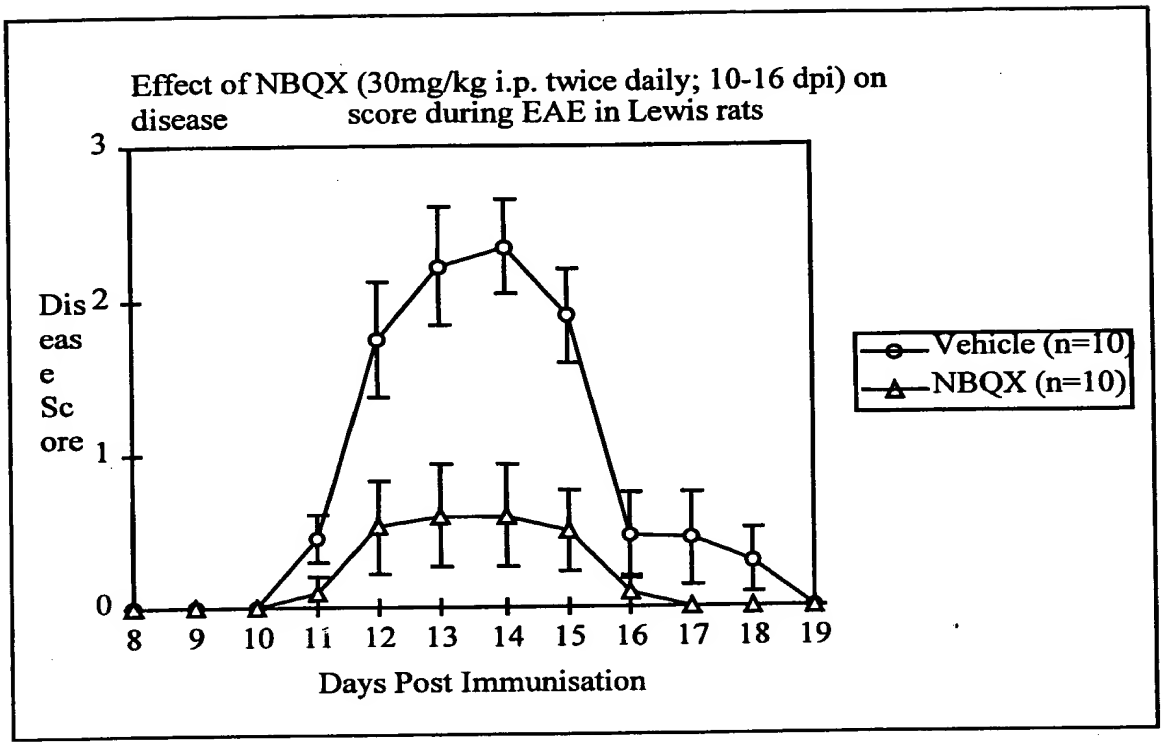

Effect of NBQX (30mg/kg i.p. twice daily; 10-16 dpi) on disease score during EAE in Lewis rats
Disease Score
3
2
1
0
8
9
10
11
12
13
14
15
16
17
18
19
Days Post Immunisation
Vehicle (n=10)
NBQX (n=10)

FIGURE 2

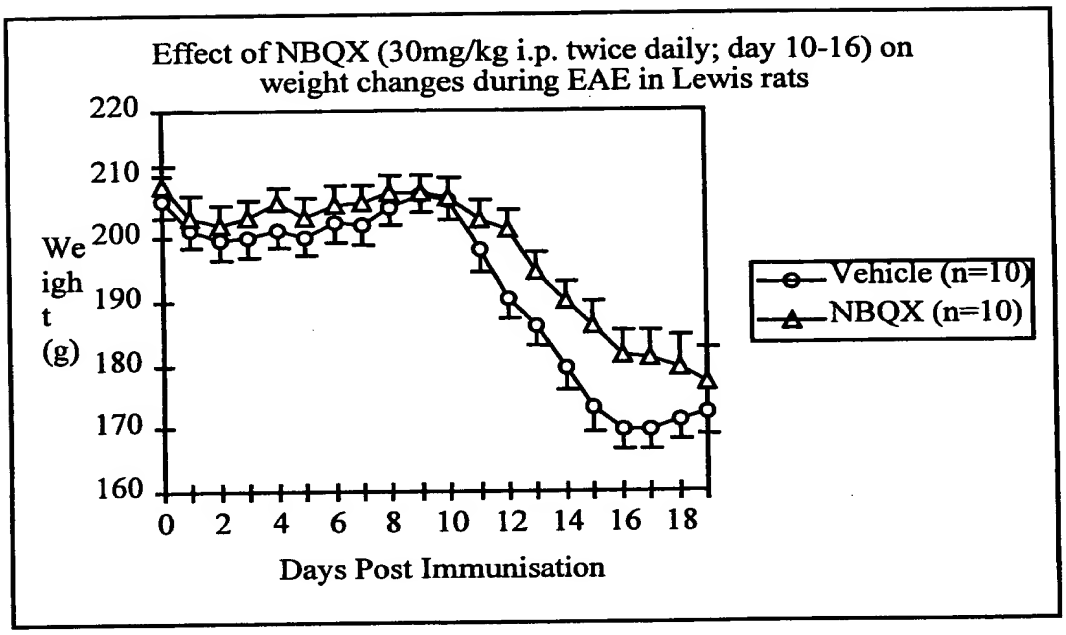
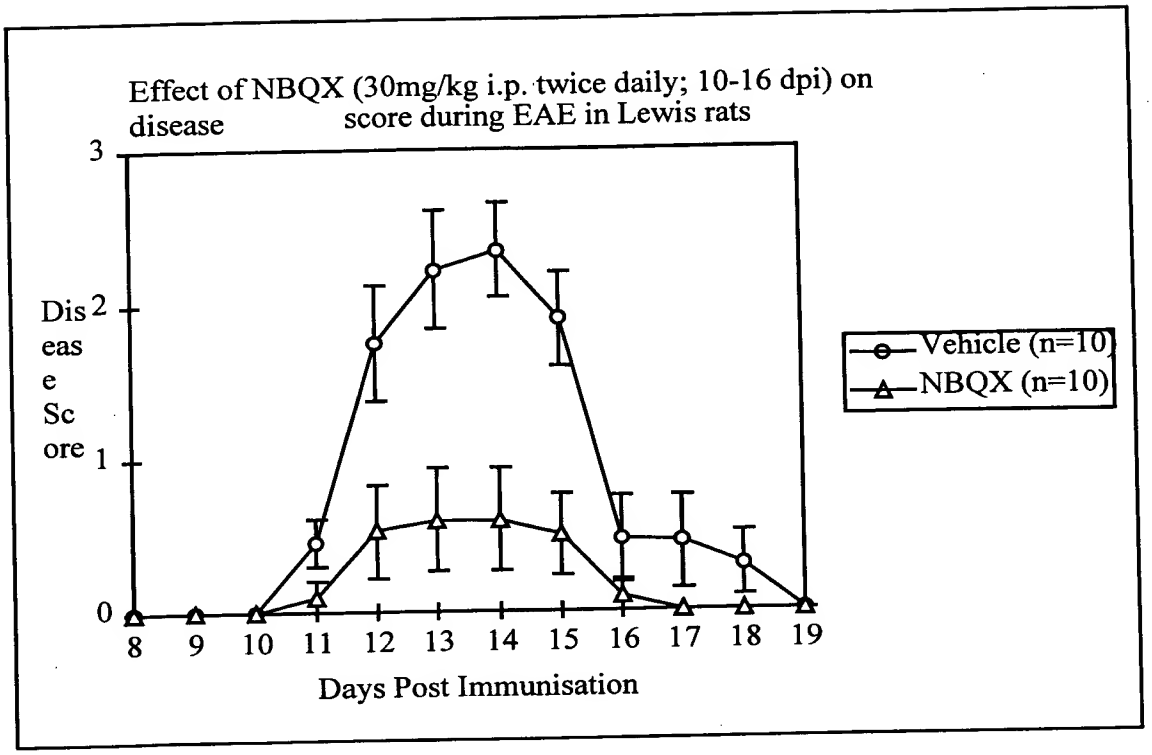

Effect of NBQX (30mg/kg i.p. twice daily; day 10-16) on weight changes during EAE in Lewis rats
Weight (g)
220
210
200
190
180
170
160
0 2 4 6 8 10 12 14 16 18
Days Post Immunisation
Vehicle (n=10)
NBQX (n=10)

FIGURE 1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15
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18
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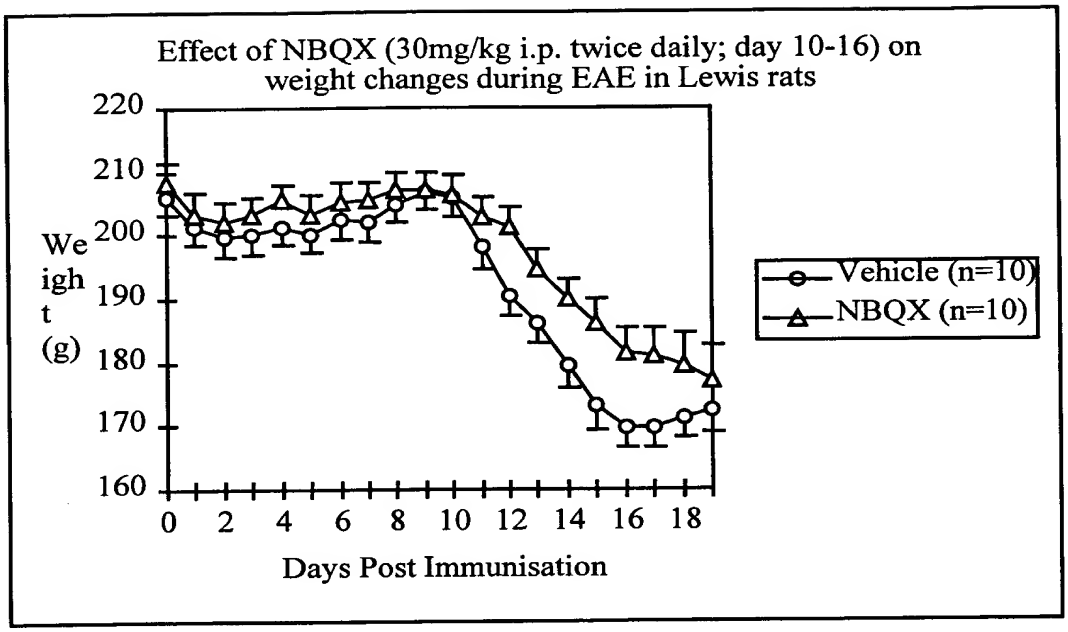
Days Post Immunisation
Vehicle (n=10)
NBQX (n=10)

FIGURE 2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16
18
Days Post Immunisation
Vehicle (n=10)
NBQX (n=10)